Lung function tests in sickle cell patients

To the editor: The interesting article by van Beers et al. states that functional studies does not offer clues as to the presence of mild pulmonary hypertension (PH) in patients with sickle cell disease (SCD) [1]. However, they did show that although not statistically significant, lung function findings do vary in hemoglobin-SS patients.

Studies examining lung function in adults with SCD conclude that pulmonary function is abnormal in 90% of patients and gradually declines over time [2,3]. The most common patterns observed were restrictive lung disease and low diffusing capacity (D_{LCO}). Few publications include data on both the D_{LCO} and the transfer coefficient (K_{CO}). However, measuring K_{CO} provides information on pathophysiology, which cannot be obtained just from the D_{LCO}. These measurements help us understand when lung disease is due to a loss of lung units (e.g., pneumonectomy), a process interfering with the alveolar surface (e.g., fibrosis) or the capillaries (e.g., PH).

Studies on patients with pulmonary arterial hypertension show that a low D_{LCO} can be used as an early marker of PH, before echocardiographic signs develop [4]. When patients with SCD are screened with echocardiogram up to 36% have evidence of PH depending on the hemoglobin genotype [5,6]. However, in autopsy studies there is histological evidence of PH in up to 75% of patients [7]. D_{LCO} may therefore be a more reliable tool than echocardiogram in predicting PH. Van Beers study shows both the D_{LCO} and K_{CO} were reduced in patients with mild PH [1].

We examined lung function results from 32 adults with SCD, average age was 34 years and 30 patients had hemoglobin-SS. The mean forced expiratory volume in 1 sec (FEV_1) was 81.8% predicted and the mean forced vital capacity (FVC) was 80.9% predicted. Two patients had an obstructive defect ($FEV_1/FVC < 70\%$) and 18 patients had a $FEV_1/FVC > 80\%$. The mean D_{LCO} (82.6% $\pm$ 3.2%) was lower than predicted but the mean K_{CO} (110.4% $\pm$ 3.2%) was higher than predicted. There was no statistical difference between patients with or without a history of acute chest syndrome. The results suggest that in these patients the pathophysiological process may be the loss of lung units.

To our knowledge, only two other studies on adults with SCD included data on K_{CO} [8,9]. These studies had similar patient numbers, characteristics and spirometry results. Unlike our study both these studies found the K_{CO} lower than predicted. This implies in these patients a different pathophysiological mechanism was operating. The difference with our patient group may be one of disease severity. The high K_{CO} we found is consistent with an increased blood flow to normal lung. A lower than predicted K_{CO} could imply the patients had developed PH, as suggested by the findings in van Beers study, or diffuse alveolar damage. Only two studies performed in children examined D_{LCO} and K_{CO} and found results similar to our study, perhaps reflecting their lower exposure to pulmonary complications [10,11].

We feel both our study and the van Beers study supports including K_{CO} and D_{LCO} in routine lung function tests to help us understand the pathophysiology and also predict early damage.

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Lung function tests in patients with sickle cell disease: A reply

To the editor: We thank Dr. Bloom and coworkers for presenting their observations and interesting hypothesis regarding the potential value of diffusion capacity (D_{LCO}) and the transfer coefficient (K_{CO} or $T_{L,CO}$ SB VA) as a early marker of pulmonary damage and sickle cell related pulmonary hypertension (PHT) in response to our recent publication [1]. Although we agree that D_{LCO} and K_{CO} could be valuable tools in understanding the pulmonary pathology of patients with sickle cell disease (SCD), several aspects merit further consideration. First, although we agree that echocardiography is not the most reliable test to diagnose PHT, it seems unlikely that the referred autopsy study [2], in which severe PHT was found in 75% of patients with SCD, is representative of patients with SCD who are nowadays screened for PHT with echocardiography. Second, though we did find a trend toward a lower D_{LCO} and K_{CO} in HbSS/Sβ^0—thalassemia patients with mild PHT when compared with HbSS/Sβ^0—thalassemia patients without PHT (D_{LCO}: 66% vs. 76% of the predicted value and K_{CO}: 99% vs. 109% of the predicted value, respectively), the observed K_{CO} values were within the normal range. In addition, a post hoc analysis of the relation of D_{LCO} and K_{CO} to tricuspid regurgitant jet flow velocity did not show a statistically significant correlation between these parameters. Delclaux et al. [3] measured the K_{CO} in a cohort of 40 patients with SCD and no significant difference was found between patients with or without PHT. Restrictive pulmonary disease is present in 35–75% of patients with SCD [4,5]. In a large study comparing total diffusion capacity and K_{CO}, it was demonstrated that restrictive pulmonary disease by extrapulmonary causes results in a lower total diffusion capacity but a higher K_{CO} when compared with healthy controls [6]. In our patients, the alveolar volume (VA) is significantly correlated to the cor to thorax ratio on chest X-ray ($r_s = -0.31$, $P = 0.028$) suggesting cardiomegaly to be an extrapulmonary cause of VA loss observed in SCD. This hypothesis would also explain observed low VA, T_{LCO} SB, and relatively high K_{CO} in SCD observed by us and others [3,7]. Taken together, we feel that that the role of D_{LCO} and K_{CO} in predicting early pulmonary damage and PHT in individual patients with SCD is limited because it may be, at least in part, the result of cardiomegaly, which is highly prevalent in patients with SCD. Moreover, the associations of PHT in SCD to renal disease, hypertension, and markers of endothelial activation indicate that SCD-related PHT should be considered a manifestation of a systemic vasculopathy [8,9].

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Pulmonary hypertension does not affect the autonomic nervous system dysfunction of sickle cell disease

To the editor: Pulmonary hypertension (PHT) is an increasingly recognized complication in patients with sickle cell disease (SCD) and may play a key role in the occurrence of sudden death [1,2]. The etiology of PHT in SCD patients is multifactorial, involving pulmonary venous hypertension, pulmonary arterial hypertension secondarily to intrinsic vasculopathy resulting from chronic hemolysis [3], endothelial dysfunction, inflammation, and hypercoagulability [4]. Some data also support that relative systemic hypertension might be a risk factor for the development of PHT [5]. The involvement of sympathetic nervous system activation was recently suggested by the exacerbation of PHT during vaso-occlusive crisis [6]. PHT in non SCD patients is associated with increased sympathetic nervous system activity [7]. There is clear evidence of autonomic nervous system (ANS) dysfunction in SCD [8–10]. ANS dysfunction is a powerful and independent predictor of severe cardiac events in an healthy population [11] and had been suggested to play a causative role in sudden death in SCD [10]. Whether ANS dysfunction is involved in PHT in SCD has never been investigated. We therefore compared indices of ANS activity in patients with homozygous sickle cell anemia (SCA) with (SCA-PHT) and without PHT (SCA-non-PHT) and in a group of healthy individuals (CONT).

A group of 66 consecutive SCA patients regularly followed by the Department of Cardiology of the Academic Hospital of Fort de France and the Integrated Center of Sickle Cell Disease of Lamentin consented to participate in the study. PHT was screened with trans-thoracic echocardiography **(**Philips iE33 system, Philips Medical Systems, Bothell, WA) as a tricuspid regurgitant jet flow velocity (TRV) $\geq$2.5 m s^{-1} [1]. Venous blood was collected for determination of hemoglobin (Hb) and serum lactate dehydrogenase (LDH) levels. Patients were submitted to a 24-hr Holter ECG monitoring (ELA Medical, Le Plessis Robinson, France). Only the night periods were analyzed (midnight to 7 A.M.) to avoid variations due to differences in the subjects' daily environment [12]. The Holter ECG data from 15 young healthy volunteers were used as the CONT group (mean age 22.7 ± 5.1 years). ANS time and frequency domain indices were derived from the RR intervals series [12]. Biological data were compared between the two SCA groups using an unpaired student' *t*-test. ANS data were compared between the three groups using a Kruskal-Wallis test and between group differences were tested with the Mann-Whitney U test. Spearman' correlations were performed in the two SCA groups between LDH and ANS data. Values are mean ± SD for biological data and median (25th, 75th) for ANS data. The significance level was defined as $P < 0.05$.

The SCA-PHT group was comprised of 10 patients with a TRV $\geq$2.5 m s^{-1} four of whom had a TRV $>$ 3.0 m s^{-1} (mean age: 43.8 ± 12.0 years vs. 37.2 ± 11.6 years in the SCA-non-PHT group). The SCA-PHT group had greater LDH levels than the SCA-non-PHT group (1011.9 ± 510.5 U/L vs. 689.3 ± 293.9 U/L, respectively; $P < 0.05$) but no significant difference was observed between the two groups for the Hb levels (7.4 ± 1.3 g/dL versus 8.4 ± 1.4 g/dL in SCA-PHT and SCA-non-PHT group, respectively) and for ANS indices (Table I). Mean RR interval is significantly decreased in the two SCA groups. SDNN, SDANN, Ptot, RMSSD, HF, and LF were significantly lower in the two SCA groups as compared to the CONT group. The LF/HF ratio of the SCA-non-PHT group was lower than the CONT group and a tendency to have lower values was also observed in the SCA-PHT group. No significant correlation was found between LDH levels and ANS indices.

As previously reported [13], our results support a higher rate of hemolysis in SCA patients with PHT as compared with SCA patients without PHT

TABLE I. Indices of the Autonomic Nervous System Activity

	CONT ($n = 15$)	SCA-non-PHT ($n = 56$)	SCA-PHT ($n = 10$)
RR interval (ms)	1,156 (1,081, 1,242)	857 (790, 896)*	879 (801, 928)*
SDNN (ms)	161.5 (148.3, 179.3)	77.2 (63.1, 97.7)*	70.3 (65.9, 77.3)*
RMSSD (ms)	106.1 (100.9, 137.3)	37.8 (26.3, 56.8)*	33.3 (27.7, 47.2)*
SDANN (ms)	73.5 (62.8, 88.4)	49.5 (39.6, 65.4)*	46.5 (35.1, 56.4)*
Ptot (ms^2/Hz)	8,820 (6,654, 9,937)	1,323 (668, 2,001)*	1,088 (992, 1,142)*
LF (ms^2/Hz)	1,249 (933.6, 1389.7)	280.0 (176.0, 480.1)*	218.3 (119.5, 328.3)*
HF (ms^2/Hz)	1710.4 (1308.9, 2648.6)	242.0 (117.2, 494.5)*	217.7 (126.7, 377.6)*
LF/HF	0.9 (0.6, 1.1)	1.7 (1.0, 2.5)*	1.5 (0.6, 1.9)

The values are obtained by time domain and frequential analyses of the RR intervals series in the control group (CONT), in patients with sickle cell anemia and pulmonary hypertension (SCA-PHT) and in patients with sickle cell anemia without pulmonary hypertension (SCA-non-PHT).
Some indices are mainly under the control of parasympathetic activity (RMSSD and HF) or reflect the global autonomic activity (SDNN, SDANN, Ptot). The low frequency index (LF) contains both sympathetic and parasympathetic activities, and the LF/HF ratio has been proposed as a marker for autonomic nervous system balance.
SDNN, standard deviation of all normal RR intervals; RMMSD, square root of the mean of the sum of the squared differences between adjacent normal RR intervals; SDANN, standard deviation of the mean of all normal RR intervals for 5-min segments (SDANN); Ptot, total power of the spectrum (Ptot, 0–0.50 Hz); LF, low frequency of the spectrum (LF, 0.04–0.15 Hz); HF, high-frequency of the spectrum (HF, 0.15–0.40 Hz).
Values are median (25th, 75th). The *P* value obtained with the Kruskall–Wallis test was always <0.001. Then, Mann–Whitney U test was used to compare CONT vs SCA-non-PHT, CONT vs. SCA-PHT, and SCA-non-PHT vs. SCA-PHT;
[a]Significantly different from the CONT group ($P < 0.001$).

but no relation has been found between the hemolytic rate and the ANS dysfunction. The comparable and very low ANS indices observed in both SCA groups indicate severely impaired global ANS activity in SCA patients independently of the presence of PHT, which may be explained by the low parasympathetic activity as compared with the CONT group. Similarly, the significantly higher LF/HF values found in the SCA groups suggest an autonomic imbalance. Although the assessment of ANS activity might be useful to identify patients at risk for cardiac complications and/or sudden death [9,10], ANS activity is not further impaired in SCA patients with PHT.

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Usefulness and limitations of Bayesian network model as a mortality risk assessment tool in sickle cell anemia

To the editor: The mutual relationship between clinical and laboratory variables in a patient with sickle cell anemia and the influence of each parameter on disease-related mortality are poorly understood [1]. To overcome this, a network model has recently been proposed to predict the risk of death [2]. This seems to be yet another promising clinical avenue for application of the Bayesian theorem and an objective assessment tool for clinicians.

In this pioneering original work by Sebastiani et al. [2], the 5-year mortality risk was projected as a disease severity score, ranging from 0 (least severe) to 1 (most severe). The authors subsequently validated the score in two separate sets of patients with sickle cell anemia and claimed accurate prediction of mortality.

We analyzed this proposed sickle cell severity score (http://155.41.217.225/dss-calculator/index.php) in an unselected cohort of patients at St George's hospital, a referral center in London for management of hemoglobinopathies. The study population included 50 adults ($\geq$18 years) to represent patients from chronic erythrocytapheresis group, well patients during outpatient clinic visits, and patients hospitalized for acute events. The patients were recruited by simple random sampling from the hospital's sickle cell disease database.

Patients were phenotypically classified as mild, intermediate, or severe based on the number of painful episodes, frequency of hospital admissions, priapism, history of stroke, acute chest syndrome or sepsis, chronic leg ulcers, pulmonary hypertension, renal impairment, and avascular necrosis of bones [3,4]. Allocation into a particular subgroup was done independently by two clinicians (PA and SC) and confirmed by a third (DHB). Discrepancies, if any, were discussed on an individual patient basis and a consensus opinion formed in each case. Baseline patient characteristics are listed in Table I. Bayesian model-based severity score for each patient was calculated from the 16 variables proposed and was compared against clinical severity. Out of 50 patients, 22 each were classified as mild and intermediate and 6 as severe. Range, mean, and median for subgroups are shown in Table II.

As our assessment was focused toward the phenotypic severity and morbidity profile of patients, we did not use variables like age, sex, or hemoglobin genotype for clinical classification of patients. We also avoided blood transfusion as an assessment variable as many of our patients declined the same because of religious beliefs. In contrast, we included renal impairment as one of the markers of disease severity, which Sebastiani et al. did not. Except for these minor differences, the parameters we selected for allocation of patients into specific clinical severity groups (mild,

TABLE I. Patient and Disease Characteristics

Variables	Number (*n*)
Mean age (range)	36.5 (18–56)
Gender (male/female)	28/22
Hb type (HbSS/HbSC/HbSβThal)	40/7/3
Hypertension (yes[a]/no)	6/44
Stroke (yes/no)	6/44
Sepsis (yes/no)	5/45
AVN (yes/no)	13/37
ACS (yes/no)	7/43
Priapism[b] (yes/no)	9/19
Mean WBC (range)	10,740/mm^3 (4,200–28,500)
Mean reticulocyte count (range)	4.22% (1.83–12.44)
Mean MCV (range)	87.5 fL (70–104.3)
Mean total bilirubin (range)	1.9 mg/dL (0.6–8.5)
Mean ALT (range)	30.7 U/L (12.7–145)
Mean LDH (range)	344 U/L (141–764)
Clinical severity (mild/intermediate/severe)	22/22/6
Mean Bayesian severity score (range)	0.19 (0.048–0.098)

[a]Average systolic BP $>$ 95th centile for age or if on antihypertensive treatment.
[b]$n = 28$ (males only).
AVN, avascular necrosis; ACS, acute chest syndrome; WBC, white blood cell; MCV, mean corpuscular volume; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.
Numerical laboratory values represent the mean of five most recent test results.

TABLE II. Break-Up of Patients According to Clinical Severity and the Bayesian Network Model Scores in Each Subgroup

Subgroup	Number	Range	Mean	Median
Mild	22	0.065–0.574	0.182	0.178
Intermediate	22	0.048–0.482	0.250	0.190
Severe	6	0.366–0.998	0.866	0.970

intermediate, and severe) are similar and comparable with those used in the original study.

Considerable overlap was noted between mild and intermediate subgroups, as was seen with the original validation cohorts of Sebastiani et al. One mild patient scored 0.574 whereas all others and intermediate patients scored below 0.5. This particular patient was 51-years-old with no painful episodes or complications. Data for LDH and reticulocyte counts, both powerful severity parameters, were unavailable. Age being a strong scoring variable, he scored much higher than that expected from clinical severity. One patient from the severe group scored 0.366 whereas all others scored above 0.8. This patient had bronchiectasis with frequent chest infections which precipitated painful episodes needing hospitalization. Being a Jehovah's witness, he had never "required" blood transfusions, another parameter which reduced the score. Thus, we found that the score is very much likely to be influenced by comorbid conditions not directly related to sickle cell disease.

We do agree that the score has high specificity and positive predictive value. The scoring system is also simple, easy to use and unambiguous. For each scoring variable except gender, there is an option "non available", so that the score can be calculated even if data on one or more variables are lacking. One obvious limitation is the high significance for increasing age. Patients above 40 years have outlived the median survival for sickle cell disease and would hence start off with a high score. If data on one or more severity parameters for such patients are unavailable, the score is likely to be spuriously high. Conversely, the accuracy of the scoring system in children needs to be investigated further. It may be recalled that in the original study by Sebastiani et al., the pediatric validation cohort had two severe patients with scores of 0.03 and 0.04.

As the authors have suggested, incorporation of genetic polymorphisms might improve the utility of the scoring system in younger patients. The score does seem to correlate with high risk for near term death and is a potential tool to help clinicians decide on more vigorous therapeutic options including stem cell transplantation.

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Cyclosporine therapy in refractory/relapsed patients with thrombotic thrombocytopenic purpura

To the editor: The optimal treatment of resistant/relapsed thrombocytopenic purpura (TTP) is not well defined. A recent Dutch study demonstrated that the frequency of recurrence in 24 patients with an acquired TTP significantly dropped after splenectomy [1]. Moreover, an increasing number of articles have been published regarding the efficacy of rituximab [2]. A recent article by Cataland and coworkers [3] regarding cyclosporine use in patients with TTP invites some considerations of the efficacy and duration of cyclosporine therapy and poses the question of whether there are some useful indicators (namely ADAMTS 13 activity and presence of inhibitors) for the correct time of cyclosporine suspension. The study reported data regarding 19 patients treated with prophylactic cyclosporine for 6 months. After discontinuing cyclosporine therapy, 10 patients remained in remission, seven relapsed, and two relapsed during prophylactic cyclosporine. Eight to nine relapsing patients had low ADAMTS 13 activity suggesting that this is a significant risk for relapse. Peyvandy et al. [4] recently found that severe ADAMTS 13 deficiency and anti-ADAMTS 13 antibody presence at the time of remission were independently associated with an approximately threefold greater likelihood of recurrence.

We treated seven patients (two refractory, five relapsed), all with ADAMTS 13 activity less than 5% (Table I), with cyclosporine initially associated with PEX. The first refractory patient (no.1) responded to cyclosporine after the failure of PEX, HDIg, and vincristine sulfate [5]. Every attempt to reduce cyclosporine showed a rapid decrease of ADAMTS 13 activity and of the platelets. The patient has now been on cyclosporine treatment without adverse events. Patient no. 2, refractory to steroids, PEX, and vincristine sulfate responded promptly to cyclosporine. Her ADAMTS 13 activity increased quickly and she did not relapse at cyclosporine discontinuation after 6 months of treatment. Among the remaining five multi-relapsed patients, patient no.3 recurred during cyclosporine assumption, showing ADAMTS 13 activity constantly less than 5% and inhibitory activity highly positive. In patient no. 4, cyclosporine constantly showed a low plasmatic level until a new relapse. Restoration of correct plasma level of cyclosporine determined a rapid clinical response and improvement of ADAMTS 13 activity with a low degree of inhibitory activity. In patient no. 5, the reduction of cyclosporine dosage determined a new recurrence, which was corrected by the increase of cyclosporine. The multi-relapsed patients, no. 6 and no. 7 responded with rapid increase of ADAMTS 13 activity.

Median follow-up of all these patients was 13 months (range: 6–132).

Our few cases seem to confirm the conclusions of Cataland and coworkers. Discontinuation of cyclosporine with low risk of relapse is possible if the ADAMTS 13 activity is stably normalized. It is probably important to maintain the correct plasmatic range of cyclosporine without reduction if ADAMTS 13 activity is not normalized. If ADAMTS 13 activity remains low, the risk of relapse is very high [6] and the patient must be strictly monitored. In responsive patients with a normal ADAMTS 13 activity, an attempt to stop cyclosporine seems possible.

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TABLE I. ADAMTS 13 and its Inhibitory Activity During Different Phases of Cyclosporine Therapy in Resistant/Relapsed TTP Patients

No. patients	ADAMTS 13 activity at the beginning of cyclosporine	Presence of anti-ADAMTS 13 auto-antibodies	ADAMTS 13 activity at response	Presence of anti-ADAMTS 13 auto-antibodies at response	Relapse	ADAMTS 13 activity at relapse	Presence of anti-ADAMTS 13 auto-antibodies at relapse
1	<5%	+	30%	Negative	After reduction of cyclosporine dosage	<5%	Negative
2	<5%	+−	60%	Negative	NO (after cyclosporine suspension)		
3	<5%	+++	<5%	+++	During cyclosporine treatment	<5%	+++
4	<5%	++	<5%	++	During cyclosporine treatment	<5%	++
5	<5%	+++	100%	Negative	After reduction of cyclosporine dosage (new response to correct dosage)	<5%	++
6	<5%	Not done	72%	Negative	NO		
7	<5%	+	93%	Negative	NO		

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Clinical efficacy of WT1 peptide vaccination in patients with acute myelogenous leukemia and myelodysplastic syndrome

To the editor: Because Wilms tumor antigen 1 (WT1) is preferentially expressed in various kinds of malignancies including acute leukemia but not normal cells, investigators are attempting to develop cellular immunotherapy for cancers targeting WT1 [1–6]. We previously identified the WT1-derived peptide that can be recognized by HLA-A*2402-restricted cytotoxic T lymphocytes (CTLs) and elicit leukemia-reactive CTLs [7–9]. A phase I clinical study of a cancer vaccine using this WT1 peptide is currently underway in our hospital. Here we report two interesting cases in which a clinical effect of WT1 peptide vaccination was detected.

The first case is chemotherapy-resistant acute myelogenous leukemia (AML) (Fig. 1A). A 72-year-old woman with de novo AML (M2) received the standard induction chemotherapy with daunorubicin and cytarabine and achieved complete remission. After 2 years, her AML relapsed and reinduction chemotherapy was performed, again resulting in complete remission. However, the AML relapsed again after 6 months, and low-dose cytarabine was administered. After this treatment, the bone marrow was normocellular, with 7% leukemic cells. The patient was then enrolled in the Phase I clinical study of WT1 peptide vaccination, as reviewed and approved by the Institutional Review Board of Ehime University Hospital. She received subcutaneous injection of 1 mg $WT1_{235\text{-}243}$ (CMTWNQMNL) peptide in Montanide adjuvant biweekly, and the WT1 peptide vaccine was administered totally 20 times. After the 5th vaccination, an aspirated bone marrow sample showed hypoplasia with less than 3% myeloblasts. The patient has since been followed up for more than 3 years. Pancytopenia and hypoplasia of the bone marrow without an increase of myeloblasts have persisted during this observation period.

The second case is a 55-year-old male with myelodysplastic syndrome (MDS) that had evolved from aplastic anemia (Fig. 1B). Despite intensive therapies, pancytopenia had persisted, and the patient had been receiving red blood cell transfusion frequently when his hemoglobin level fell to less than 6.0 g/dL. When this patient was enrolled in the WT1 peptide vaccine trial, bone marrow aspiration revealed normoplasia with 2.2% myeloblasts and a slightly increased expression level of WT1 mRNA. After vaccination with 1 mg WT1 peptide, the hemoglobin level gradually increased and the WT1 mRNA level in bone marrow cells decreased to within the normal range. The patient was vaccinated with WT1 peptide totally 30 times, and has been followed up for more than 3 years. His hemoglobin level has been maintained at more than 7.0 g/dL, and no red blood cell transfusion has been required during WT1 peptide vaccination.

The data of $WT1_{235\text{-}243}$/HLA-A*2402 tetramer assay for monitoring WT1-specific CTLs was shown in Fig. 2. Since we could not detect WT1-specific CTLs apparently when freshly isolated lymphocytes were used for assays, peripheral blood mononuclear cells were stimulated with $WT1_{235\text{-}243}$ peptide in vitro and then analyzed. WT1-specific CTLs were not detected in peripheral blood of both patients before WT1 peptide vaccination, and were apparently detected after the 3rd or 4th vaccination. $WT1_{235\text{-}243}$-specific CTL lines were generated by stimulation of peripheral blood lymphocytes from these patients with WT1 peptide in vitro (data not shown).

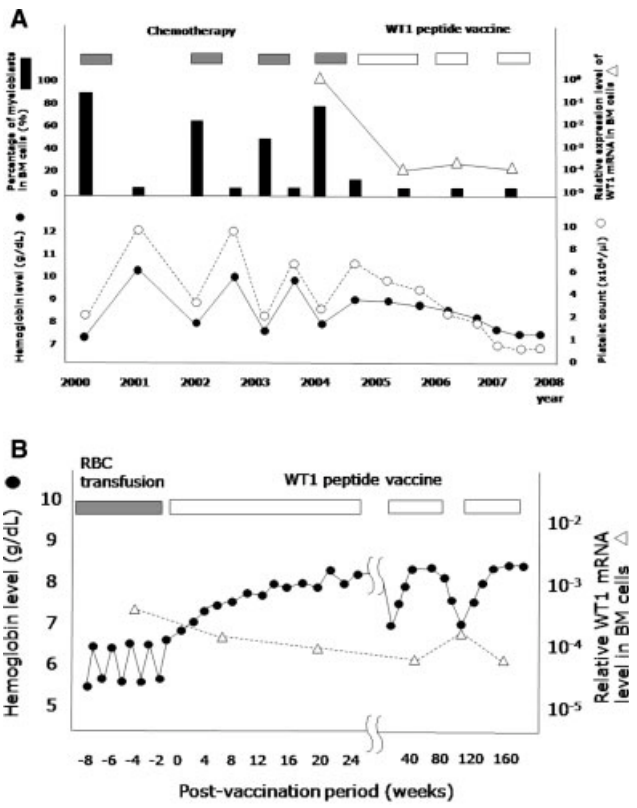

Fig. 1. Clinical efficacy of WT1 peptide vaccination. (A) Clinical course of the patient with AML. Pancytopenia and hypoplasia of bone marrow occurred, but the leukemia cells did not proliferate after WT1 peptide vaccination. (B) Clinical course of the patient with MDS. The hemoglobin level increased gradually after WT1 peptide vaccination and decreased during discontinuance of vaccination.

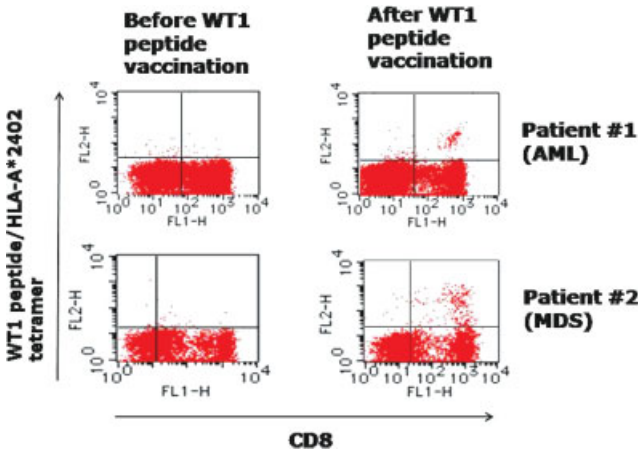

Fig. 2. Tetramer assays for detection of $WT1_{235\text{-}243}$-specific CTLs. Peripheral blood mononuclear cells isolated from the patients were stimulated with $WT1_{235\text{-}243}$ peptide in vitro and then stained with $WT1_{235\text{-}243}$/HLA-A*2402 tetramer. WT1-specific CTLs were detected in peripheral blood of the patients after WT1 peptide vaccination. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

In the first patient with AML, pancytopenia was developed following WT1 peptide vaccination. The hypothesis that normal hematopoietic stem cells as well as leukemia cells were also damaged by WT1-specific CTLs seems unlikely to be by the following reasons. The first is that WT1-specific CTLs were increased after the 5th vaccination resulting in the decrease of myeloblasts, but at this time normal hematopoiesis was not significantly damaged. The second reason is that the other clinical studies using WT1 peptide vaccination showed that WT1-specific CTLs did not damage normal hematopoiesis. One of the possibilities is that this AML case might have a component of MDS and that WT1-expressing transformed stem cells, from which erythrocytes and platelets were derived, were damaged by WT1-specific CTLs, resulting in pancytopenia as reported previously in a case of MDS-derived AML [10]. The mechanism responsible for the improvement of anemia in the second patient with MDS is unclear, but it is speculated that WT1-specific CTLs may have lysed abnormal clone cells that had inhibited normal hematopoiesis. Taken together with papers previously published [2,3,5,10], our data indicate that immunotherapy targeting WT1 might be promising; however, precise monitoring of hematopoiesis in vaccinated patients is important.

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Effective treatment for *de novo* hepatitis B with nucleotide analogue in patients with hematological malignancies

To the editor: Individuals with resolved hepatitis B, characterized as hepatitis B surface antigen (HBsAg)-negative and hepatitis B core antibody (anti-HBc)-positive, have latent hepatitis B virus (HBV) infection in their liver tissue [1–3]. Cytotoxic chemotherapy and hematopoietic stem cell transplantation sometimes trigger the reactivation of latently infected HBV, resulting in *de novo* hepatitis B [4–6]. Although *de novo* hepatitis B could cause acute liver failure or chronic hepatitis, an effective management strategy for *de novo* hepatitis B has not been well established. The benefit of prophylactic antiviral therapy to HBsAg-negative but anti-HBc-positive patients remains controversial, because HBV activation is infrequent and there is not enough information to recommend routine prophylaxis at this time [7,8]. We report two patients of *de novo* hepatitis B after treatment for malignant lymphoma who were treated by nucleotide analogues. Nucleotide analogue treatment immediately after the occurrence of *de novo* hepatitis B resolved the hepatitis and induced clearance of serum HBsAg and HBV DNA in both patients. Notably, both patients remained negative for HBsAg and HBV DNA in their serum even after termination of nucleotide analogue treatment.

Patient 1. A 62-year-old man first presented with abdominal pain. Gastroscopy showed an ulcerative lesion at the fornix of the stomach. An endoscopic biopsy of the ulcerative lesion showed diffuse large B cell lymphoma. He was treated with six cycles of EPOCH chemotherapy (etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin) with rituximab followed by one course of R-CHOP chemotherapy (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone) and then received autologous peripheral blood stem cell transplantation (auto-PBSCT) 10 months after diagnosis. He achieved complete remission.

Before auto-PBSCT, he was negative for HBsAg but positive for hepatitis B surface antibody (anti-HBs) and anti-HBc. After auto-PBSCT, we again confirmed that he was negative for HBsAg and hepatitis Be antigen (HBeAg) but positive for anti-HBs and anti-HBc. A sensitive polymerase chain reaction assay revealed no evidence of HBV DNA in his serum. Although his serum alanine aminotransferase (ALT) level was within normal limits until 8 months after auto-PBSCT, it increased to 252 IU/ml during the next month. Coincident with the elevation of ALT level, he became positive for HBsAg and HBeAg but negative for anti-HBs. At that stage, his serum HBV DNA level was $10^{7.3}$ copies/ml. He was diagnosed with *de novo* hepatitis B and lamivudine therapy (100 mg/day) was started 7 days after the elevation in ALT. Twenty-nine days after the initiation of lamivudine treatment, he was negative for HBsAg and his serum level of HBV DNA had decreased to $10^{4.6}$ copies/ml. After 105 days of lamivudine treatment, serum HBV DNA was undetectable and he was negative for HBeAg. Because he acquired anti-HBs and hepatitis Be antibody (anti-HBe) in his serum, lamivudine treat-

ment was stopped 5 months after the initiation of the treatment. He remained negative for HBsAg and HBV DNA and his ALT level was normal during a follow-up visit 2 years after withdrawal of lamivudine.

Patient 2. A 43-year-old woman first presented with cervical lymphadenopathy. Histopathological examination of the cervical lymph node demonstrated diffuse large B-cell lymphoma. She was treated with six cycles of EPOCH chemotherapy (etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin) with rituximab and achieved complete remission. She then received auto-PBSCT. Seven months after auto-PBSCT, she relapsed with lymphoma of the central nervous system and received three cycles of ICE chemotherapy (ifosfamide, carboplatin, and etoposide) with rituximab and two cycles of high-dose methotrexate/ara-C treatment. Although she achieved complete remission again, she had a second relapse of lymphoma 6 months after the first relapse. She was treated with GDP (gemcitabine, dexamethasone, and cisplatin) with rituximab and received an allogeneic bone marrow transplant (allo-BMT) from unrelated donors in next month of the second relapse. She remained in complete remission for 16 months after the allo-BMT but then had a third relapse of lymphoma. She received two cycles of GDP chemotherapy with rituximab and achieved complete remission.

Before auto-PBSCT, she was negative for HBsAg and HBeAg but positive for anti-HBs, anti-HBc, and anti-HBe. Serum HBV DNA was undetectable. Her serum ALT level was normal to slightly elevated (32–53 IU/l) until 16 months after allo-BMT, but during the next month it suddenly increased to 1497 IU/l. She was positive for HBsAg and HBeAg, negative for anti-HBs and anti-HBe, and her serum HBV DNA level was $10^{7.4}$ copies/ml, suggesting that she had developed *de novo* hepatitis B. Entecavir therapy (0.5 mg/day) was commenced on the day of ALT elevation. Fifty-six days after initiating entecavir treatment, she was negative for HBsAg and her serum HBV DNA had decreased to an undetectable level. Because she was treated with GDP and rituximab from 2 months after HBV activation for her third lymphoma relapse, entecavir administration had been continued to prevent HBV reactivation for 8 months. Then, entecavir administration was stopped after confirming the stable negativity of HBsAg. Serum HBsAg and HBV DNA remained negative during the follow-up period 3 months after the termination of entecavir treatment.

In conclusion, nucleotide analogue treatment during the acute phase of *de novo* hepatitis B resulted in complete clearance of both HBsAg and HBV DNA from serum in patients who received chemotherapy and hematopoietic stem cell transplantation for hematological malignancies. Early administration of nucleotide analogues should be important to avoid the development of acute liver failure or chronic hepatitis B.

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Postsplenectomy vascular complications: Feasibility of studying patients with splenectomy following trauma

To the editor: Total splenectomy has been associated with several long-term complications, the most feared of which is overwhelming postsplenectomy infection. More recently, vascular complications, such as pulmonary arterial hypertension [1,2], deep venous thrombosis [3,4], and atherothrombosis [5] have gained attention. Such vascular complications have been documented following splenectomy in various hemolytic disorders [6], but these findings may be confounded by persistent intravascular hemolysis. There is some evidence in individuals who have undergone splenectomy for nonhematologic indications that the lack of a spleen, rather than intravascular hemolysis, may be the primary cause of vascular complications [7], but further investigation is needed.

We therefore sought to determine the feasibility of conducting a study of vascular complications following splenectomy for trauma. We hypothesized that as trauma is one of the major indications for splenectomy, sufficient numbers of such patients might be available for follow-up to investigate the long-term effects of splenectomy without the confounders of hemolytic disease or chronic illness.

We performed a retrospective chart review of patients who had a total splenectomy between 1992 and 2006 at Parkland Memorial Hospital (PMH), the Dallas, TX metropolitan area's primary trauma center. Hospital medical records, trauma registry, and a professional billing compilation database were searched using the ICD-9-CM Procedure Code (41.5) and Current Procedural Terminology codes (38100, 38102, 38120) for total splenectomy. Because of our interest in the current health status of patients following splenectomy, records from patients having splenectomy during 2003 and 2004 were used to conduct a more focused comprehensive chart review. We sought the following data for each of these patients: demographics, indication for splenectomy, duration of follow-up at PMH, follow-up data regarding subsequent vascular events, and laboratory test results potentially associated with increased risk of vascular complications.

Our analysis determined that 855 patients underwent total splenectomy between 1992 and 2006. Of these, 643 (75%) procedures were performed following trauma (Fig. 1). In 2003 and 2004, there were 117 total splenectomies (77 were due to trauma). No records were available for four patients, and 20 of the 77 died from their multiple injuries shortly after hospitalization. The 53 remaining subjects had a median age of 30 years (range 14–

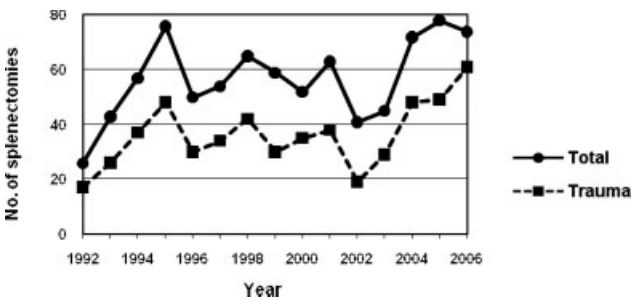

Fig. 1. Total splenectomies (total number and number following trauma) performed annually at Parkland Memorial Hospital, Dallas, TX, during the years 1992–2006.

65 years) and 49% were discharged in good condition, whereas the other 51% had extensive injuries or continuing medical conditions at discharge. Unfortunately, we found only 9 of the 53 (17%) patients had any laboratory data recorded greater than 6 months after splenectomy. Of these patients, three appeared well, whereas the other six had serious confounding complications.

Although total splenectomy following trauma continues to be a common procedure at PMH, our retrospective review does not yield adequate numbers of subjects to retrospectively evaluate postsplenectomy complications in the long term. There are several reasons for this. First, because nonoperative management of splenic injury is preferred, patients who do have total splenectomy due to trauma often have extensive injuries that are fatal or severely debilitating. If the person survives, any potential investigation of vascular complications specifically as a result of splenectomy would likely be confounded by the chronic morbidity resulting from such major trauma. Moreover, patients who are well postsplenectomy do not typically seek routine follow-up care at a trauma center such as PMH but instead return to their primary physician.

Efforts to investigate long-term complications of splenectomy should continue, as there does appear to be a link between the spleen's filtering function and vascular health. Robinette and Fraumeni found excess mortality from ischemic heart disease among US servicemen who had splenectomy due to trauma [7]. In addition, Schilling made the remarkable observation that patients with hereditary spherocytosis who underwent splenectomy were 5.9 times more likely to experience an arteriosclerotic event when compared with HS patients with intact spleens [5]. Recent investigations have also found splenectomy to be a possible risk factor in the development of pulmonary arterial hypertension [1,2].

In conclusion, although we found that a retrospective study was not feasible, sizable numbers of patients undergo splenectomy at primary trauma centers. Therefore, a prospective study of patients with splenectomy due to trauma—in collaboration with emergency department and trauma staff—could be performed to assess the incidence, timing, and mechanisms of vascular complications.

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The influence of treatment in specialized centers on survival of patients with thalassemia major

To the editor: Several countries have reported improved survival of patients with thalassemia major [1–4]. This has been attributed to better transfusion therapy, more adequate chelation [5–7], the availability of magnetic resonance for the evaluation of cardiac iron overload [8], and the referral of patients to centers of excellence. Patients from our clinic were included in a cohort previously described [1,9–13]. Here, we report the survival data from the Liguria Thalassemia Major Registry. This registry, collected in WebThal®, an electronic clinical records system designed for Thalassemia, has been maintained at the Galliera Hospital in Genova, Italy, since 1975, to record births, deaths, and causes of death of patients with thalassemia major who reside in the Liguria region of northwest Italy. In this region, there are two specialized centers: the Galliera Hospital Center practices a global approach to hemoglobinopathies, and the Gaslini Hospital Center focuses on general hematological pediatrics with considerable expertise in treating thalassemia. For convenience, and in the belief that transfusion and chelation could be prescribed by any competent physician, some patients were treated and followed in other pediatric or transfusional centers. All patients were prescribed with a similar regimen of pretransfusional hemoglobin, hemocomponent, and chelation therapy. Because the registry is updated annually, we were able to compare the survival data for patients born in the period 1970–1980 and referred to specialized centers (IC) with that of patients referred elsewhere (OC). Of a total number of 50 patients, 41 were in the IC group and 9 in the OC group. Overall, there were no significant differences in gender distribution (26 males and 24 females). In the OC group itself, however, there were more males than females (IC: male 19, female 22; OC: male 7, female 2).

Figure 1 shows the comparison of the Kaplan–Meier estimates of the cumulative probability of death, which is defined as the time from birth to the date of death or of the last follow-up visit for the two groups of patients. The survival curve of the IC patients is very similar to that published by Borgna-Pignatti et al. [12]. All OC patients, however, died at or before the age of 23. As previously described [12], males had a worse prognosis than females. Cox regression analysis, after adjusting for sex, indicated that the OC patients had a hazard ratio equal to 18.1 (95% confidence interval = 4.7–69.0; $P < 0.001$). In the IC group, the main causes of death were cardiac failure followed by infection (as reported by Borgna-Pignatti et al.) [1,12]. All of the OC patients died of acute congestive heart failure.

It is probable that increased survival rates for patients treated in specialized thalassemia centers are explained by the greater availability [14] and precision of chelation, more adequate control of compliance, and more adequate therapy for complications, especially heart failure and arrhythmias.

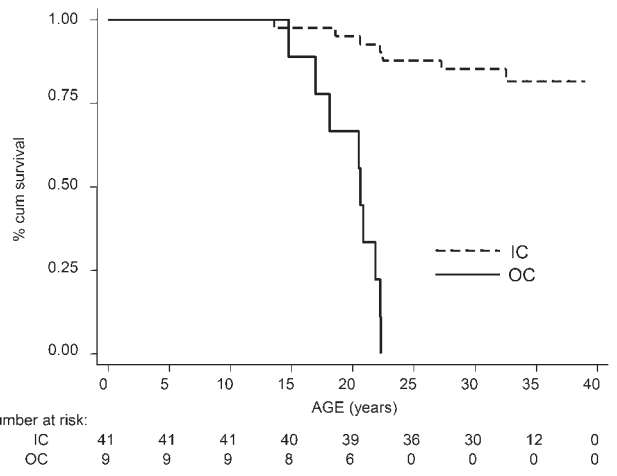

Fig. 1. Kaplan–Meier overall survival curves of patients referred to specialized centers (IC) versus patients referred to nonspecialized centers (OC). Log-rank *P*-value < 0.0001; hazard ratio of OC versus IC adjusted for sex (Cox model): 18.1, 95% confidence interval = 4.7–69.0; $P < 0.001$.

This would explain the differences between survival curves obtained for Italian [12] and English patients [8] in previous studies. In the first case, all patients were referred to specialized centers, whereas in the second, patients were treated in a variety of centers, some that are specialized in treating thalassemia and some that do not.

Our results confirm that treatment in specialized centers is necessary to guarantee the best care for patients with thalassemia. If patients with thalassemia cannot be treated in specialized centers, intensive training should be offered to care providers for these patients.

In conclusion, treatment of patients with thalassemia major in specialized centers of excellence plays an important role in improving their overall survival.

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