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Title: A case of pulmonary asbestosis presenting with temporal arteritis which involved multiple medium-sized vessels

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Abstract

A 76-year-old woman with pulmonary asbestosis was admitted with fever and polymyalgia. She subsequently developed a visual disorder, hemoptysis, and hemoperitoneum. A biopsy of the temporal artery revealed the presence of giant cell arteritis. CT and angiography showed hemorrhaging from the bronchial and abdominal arteries. These observations suggested temporal arteritis in which medium-sized vessels were involved. This case implies the association between vasculitis and asbestosis, and suggests a problem in the classification of vasculitides.

Introduction

Systemic vasculitis is a systemic autoimmune disorder, whose etiology is still largely unknown. Although many efforts have been made to clarify the pathogenesis, environmental factors such as inhalational or industrial materials has not been well focused on before recent investigations showing the existence of a relationship between vasculitis and silicosis[1-6]. Asbestos is also a critical material which can induce pneumoconiosis, pleural plaques, lung cancer and malignant mesothelioma. Although the association of asbestos with immunity has been investigated, quite a few studies provided insight into the relationship between asbestos and vasculitis[7-9].

The current classification of vasculitis syndrome, defined at the Chapel Hill Conference, is based upon the size of the suffering vessels and/or upon the detection of anti-neutrophil cytoplasmic-antibody (ANCA)[10], which has provided a definitive description especially in small-sized vessel vasculitis[11]. In contrast, since the diagnosis is still largely dependent on characteristic epidemiologic manifestations[12] in large and medium-sized vessel vasculitides, diagnostic confusion often occurs in atypical cases.

Here, we describe a case of pulmonary asbestosis presenting with temporal arteritis with atypical manifestations, hemoptysis and hemoperitoneum.

Case Report

A 76-year-old female with a 10-year history of asbestos exposure developed a low-grade fever, mild dyspnea on effort, dry cough, and polymyalgia. She visited several clinics and eventually chest computed tomography (CT) indicated pulmonary fibrosis. Oral glucocorticoids were administered (initially 20 mg of daily prednisolone) for half a year before her initial visit to our hospital. Though dyspnea, cough, and pulmonary symptoms had not improved, fever and polymyalgia were dramatically reduced. However, because she again developed slight fever and mild polymyalgia while tapering glucocorticoids, she was referred to our hospital. Chest X-ray and chest CT showed reticular and/or reticulo-nodular shadows in both lungs, indicating pulmonary fibrosis (**Fig. 1a, b**). We performed bronchoscopy on her, and several asbestos bodies were detected in her bronchoalveolar lavage fluid (BALF) (**Fig. 1c**). Transbronchial lung biopsy (TBLB) specimens showed non-specific parenchymal fibrosis. Our final diagnosis was pneumoconiosis due to asbestos exposure, thus dose of glucocorticoids was reduced and finally discontinued. Two weeks after the termination of glucocorticoids, she developed a spiking fever and a severe polymyalgia located in the proximal portion of both upper and lower limbs, and then, was admitted to our hospital. Laboratory test results are shown in **Table 1**. Tests showed her C-reactive protein (CRP) value to be greater than 20 mg/dl and she had elevated erythrocyte sedimentation rate (ESR) with leukocytosis, as well as a positive-test for rheumatoid factor (RF) and low tittered positive-test for MPO-ANCA. Anti-nuclear antibody (ANA) was negative. She displayed

slight fine crackles on both sides of the lower back chest and mild pitting edema on both upper and lower limbs. Severe myalgia and a strong inflammatory response made us consider the presence of polymyalgia rheumatica (PMR), however, no other causative factors, such as infection, an adverse reaction to drugs, and the presence of neoplasms, were detectable. On the following day, she suddenly complained of right-sided visual abnormality resulting from central retinal artery occlusion that was detected ophthalmoscopically in her right eye. A biopsy of right temporal artery was performed, and the specimen showed infiltration of inflammatory cells with giant cells (**Fig. 2**) and thus we made a diagnosis of temporal arteritis (TA). Immediately, she was administered glucocorticoids pulse therapy (intravenous 500 mg of methylprednisolone for three days) followed by 40 mg daily of oral prednisolone. Spiking fever and polymyalgia disappeared and CRP was depressed after starting treatment. However, she developed hemoptysis on the seventh hospital day. Chest CT showed a shadow, assumed to be a hematoma and the origin of bleeding, in the right middle lobar bronchus. Because widespread ground-glass opacity was not accompanied, the hemoptysis was suspected to be due to a rupture of the bronchial artery rather than an alveolar hemorrhage (**Fig. 3**). With the application of hemostatics, hemoptysis was attenuated, however, hemorrhagic shock with hemoperitoneum (**Fig. 4**) suddenly appeared on the following day. Abdominal arterial angiography showed a ruptured aneurysm in the left gastric artery, which was treated with coil-embolization. Since her pathophysiological status indicated classical polyarteritis nodosa (cPN)-like multiple systemic vasculitis, daily oral

cyclophosphamide (100mg daily) was administered along with the prednisolone, as soon as her blood pressure and other vital signs were determined to have stabilized. No further complications were observed and she was discharged from our hospital. Her condition is presently monitored on an outpatient basis.

Discussion

This report presents a case of pulmonary asbestosis showing temporal arteritis with bronchial and abdominal hemorrhage, indicating the involvement of visceral arteries.

Recent investigations have shown a possible association between environmental materials and systemic vasculitis[4, 5]. Especially, silica is focused on as a causative factor for developing ANCA-associated angiitis[2, 6]. On the other hand, though asbestos is also a major material triggering pneumoconiosis as silica, the association between asbestos and vasculitis is controversial. Since the 1960s, the relationship between asbestosis and autoimmunity has been discussed[8]. RF and ANA were reported to be associated with asbestos exposure[13]. Pelclova and colleages reported that MPO-ANCA positivity was higher in those who had exposed to asbestos. Philteos and Inoue reported cases of microscopic polyanngiitis possiblly associated with asbestosis[2, 14]. However, although Rihova described a clear association between silica and ANCA-associated vasculitis, the association between asbestos and vasculitis was not confirmed. It is true that the picture of pneumoconiosis of silica and that of asbestos are different. Silicosis is characterized with calcification whereas asbestosis is characterized with carcinogenesis. Such a difference may be due to the immunological dissimilarity. Wu reported the difference between silica and asbestos in the view of CD69, a cell surface antigen, expression[15]. In the present case, positive tests for RF and ANCA were observed, and these markers decreased to the normal

range in line with the resolution of fever and the diminishment in serum CRP level following immunosuppressant therapy. Although the association of RF and ANCA with neither temporal arteritis nor cPN has been confirmed, these markers seemed to be linked with the disease activity in this patient. It was obvious that this patient had underlying immunological abnormalities as evidenced by the presence of autoantibodies, and there was also a possibility that exposure to asbestos might have induced these abnormalities. However, to the best of our knowledge, no case of large vessel vasculitis accompanying pulmonary asbestosis has ever been previously reported.

In the present classification[10], accurate discrimination between large vessel vasculitis and medium-sized vessel vasculitis is complicated because the border between large and medium-sized vessels is ambiguous. Furthermore, large vessel vasculitis often involves not only large but also medium-sized vessel, and *vice versa*. Temporal arteritis is pathologically characterized by GCA. Thus, "temporal arteritis" and "GCA" are often used to indicate the same disease[16]. On the other hand, PN is characterized by necrotizing vasculitis in multiple medium-sized vessels[12]. However, previous reports showed that necrotizing vasculitis could occur in the temporal artery, and inflammation of the temporal arteritis could occur in systemic necrotizing vasculitis patient[17-19]. Therefore, it is impossible to distinguish GCA from necrotizing vasculitis without biopsy of the temporal artery[19].

First, the condition of the present case was recognized as typical temporal arteritis when GCA was observed in biopsy specimen of the temporal artery. Accompanying visual dysfunction, which is also a typical symptom in temporal arteritis, supported this recognition. However, bronchial and abdominal involvements, which are rarely reported in cases of temporal arteritis[20], appeared after initiating glucocorticoids. Because the lesions were assumed to be multiple medium-sized visceral vessels, which are rather typical in cPN, a diagnosis of "multiple systemic vasculitis" was made, thus leading to the administration of cyclophosphamide. Unfortunately, because the bronchial and abdominal lesions were not histopathologically verified, the presence of either granulomatous GCA or necrotizing vasculitis in bronchial artery and left gastric artery could not be determined. Although histological proof was not obtained, we believe that both temporal and visceral lesions have a similar etiology because the series of vascular events occurred within several days after beginning of her symptoms related to severe inflammation. The presence of congenital vascular deformity as a cause of vascular rupture cannot be excluded, however it is an extremely rare disease and merely accompanies inflammation. We therefore concluded that this patient had visceral arterial vasculitis as well as temporal arteritis and added cyclophosphamide. This case might suggest that temporal arteritis should be divided into two groups; with or without extracephalic lesions. In the former cases, it should be considered to add immunosuppressants on glucocorticoids.

This case showed hemorrhage, which is rather atypical in cPN and in temporal arteritis, as well as occlusive symptoms. Interestingly, the hemorrhage appeared after initiating glucocorticoids and the addition of cyclophosphamide appeared to effectively manage it. Temporal arteritis is generally controllable with steroid therapy, thus, the inflammation in her vessels seemed to contain a condition requiring immunosuppressant.

Since terminological or conceptual confusions still exist in systemic vasculitis, a better pathological or ethiological understanding of vasculitis is required for optimal clinical application. This case reflected a possible association of asbestos and the deficiencies in the current classification of systemic vasculitis, also provide information to consider more precise pathogenesis and classifications to avoid confusions in large and medium-sized vasculitis.

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Figure Legends

Fig. 1. Chest X-ray (**a**) and CT (**b**) at the first visit to our hospital. Reticular and/or reticulo-nodular shadows in both lungs were observed. Asbestos body (**c**) was detected in the BALF.

Fig. 2. Hematoxylin-Eosin staining of right temporal artery biopsy specimen. Left picture, with 40-fold magnification, shows many inflammatory cells infiltrating into the vessel wall of temporal artery and ruptured internal erastic membrane. Right picture, with 100-fold magnification, shows giant cell formation.

Fig. 3. Chest CT after hemoptysis. A low density intrabronchial shadow (arrow head) in right middle lobar bronchus, which was supposed the origin of bleeding, without widespread ground-glass opacity, thus indicating that hemoptysis was due to a rupture of the bronchial artery rather than due to alveolar hemorrhaging

Fig. 4. Abdominal CT after hemoperitoneum and hypovolemic shock. Abdominal arterial angiography showed a rupture of the aneurysm in the left gastric artery (arrow head), which was treated with coil-embolization.

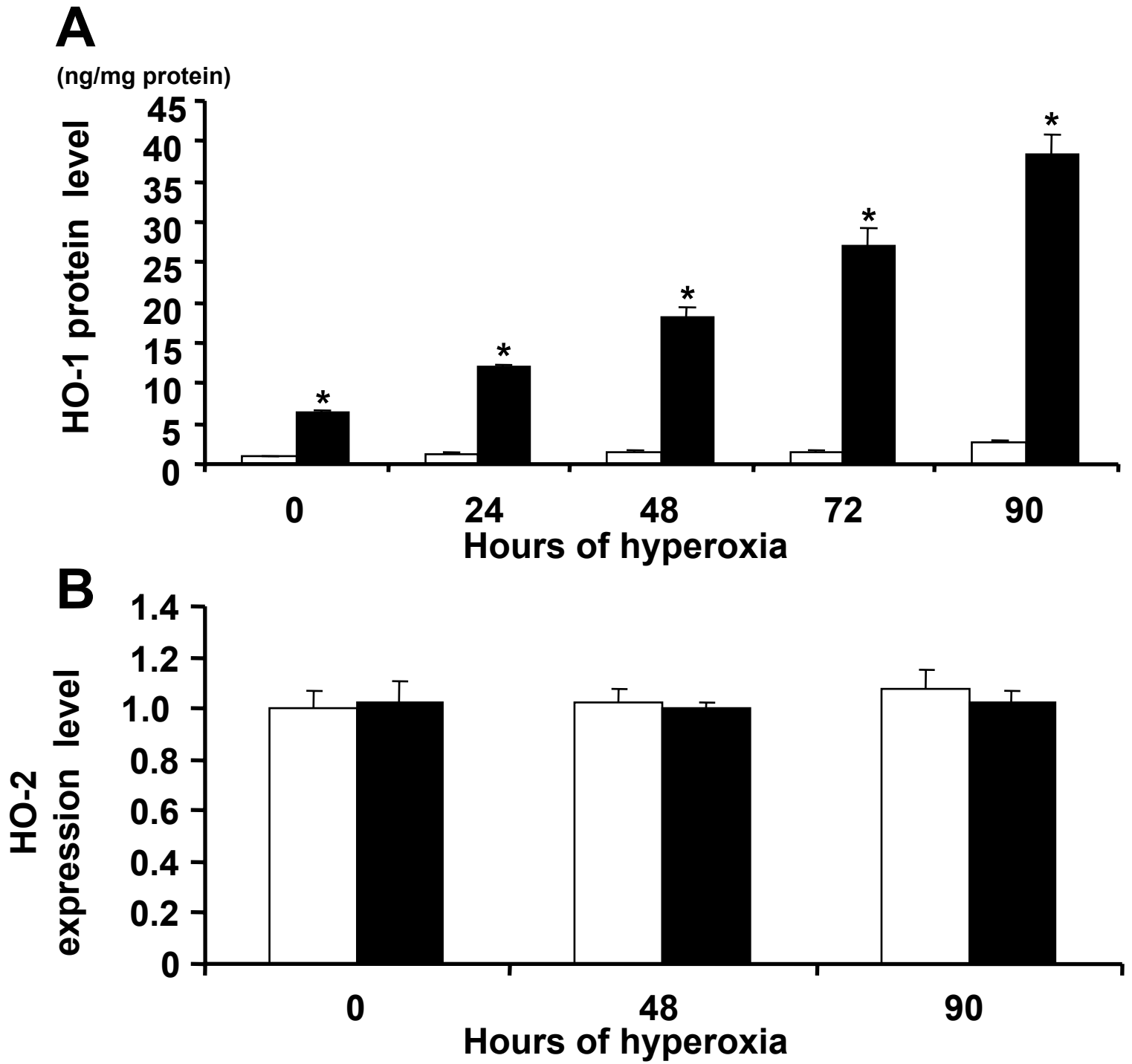
Table 1. Laboratory findings on admission.

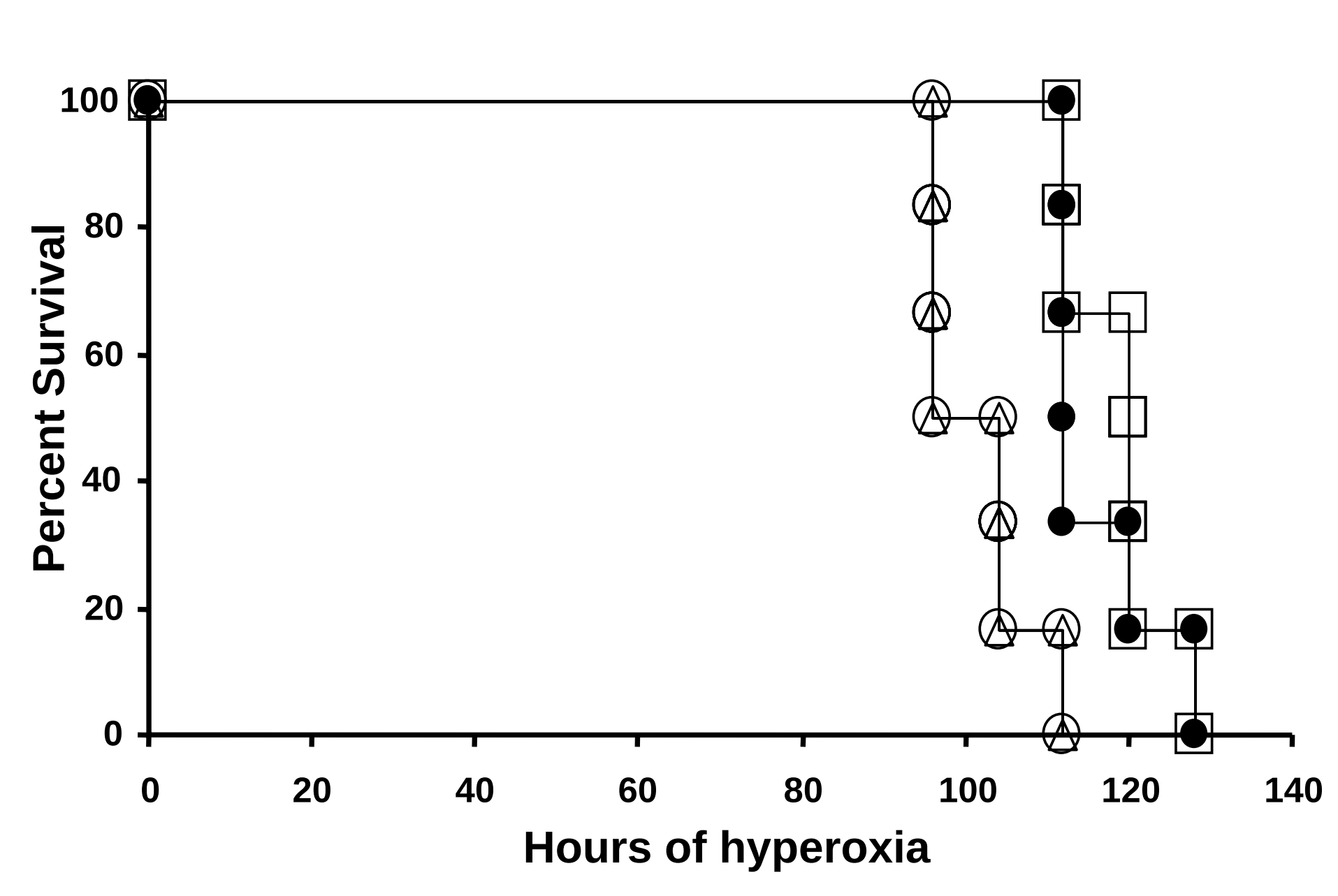
Table 1. Laboratory Findings

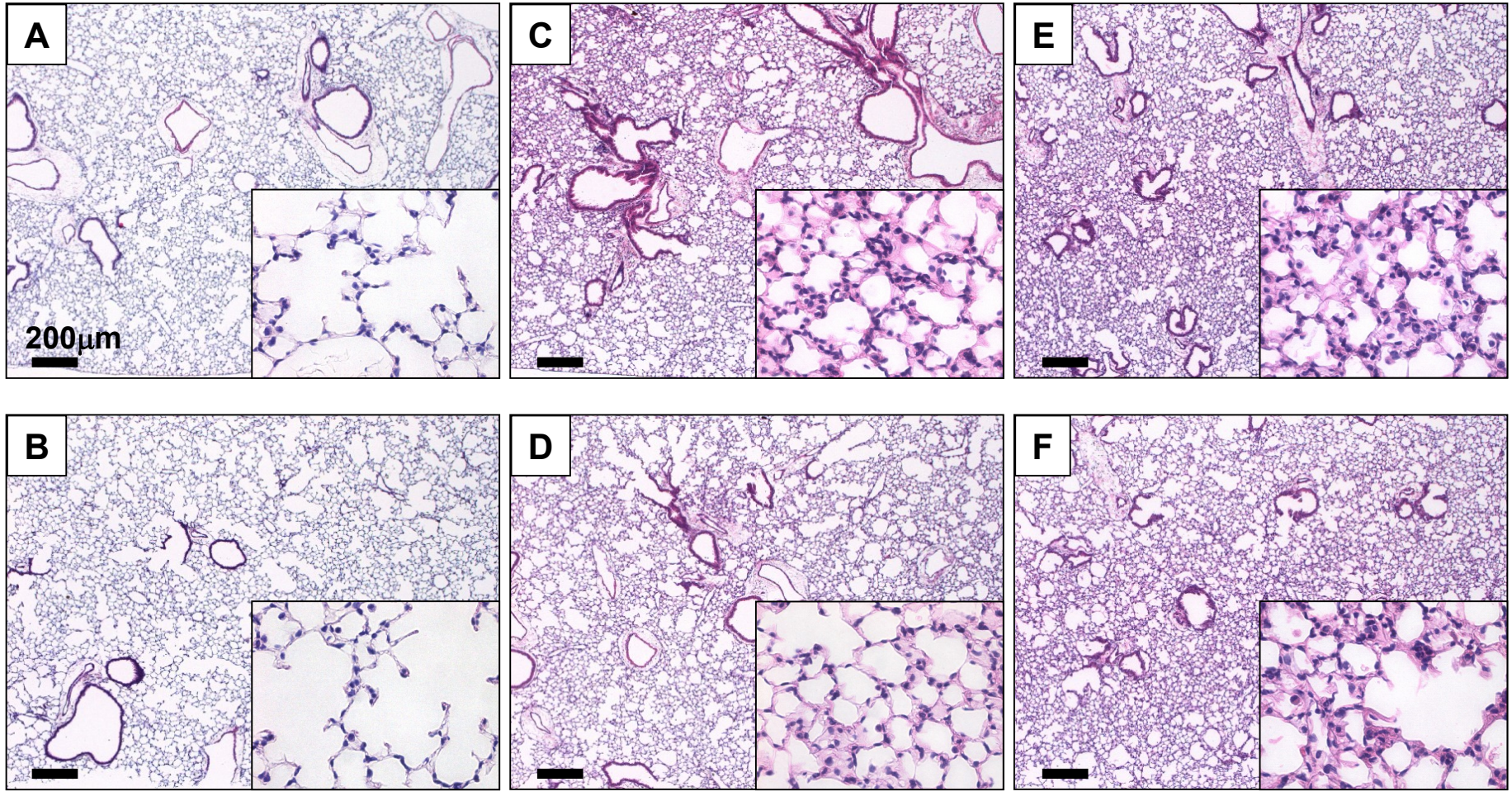
ESR	95	mm
Occult blood (stool)	negative	
Urinalysis		
Protein	(-)	
Occult blood	(-)	
Sediments	normal	
CBC		
WBC	22,200	/ μl
Ne	88.5	%
Ly	5.7	%
Mo	4.1	%
Eo	1.6	%
Ba	0.1	%
RBC	327×104	/ μl
Hb	8.6	g/ dl
Hct	27	%
Plt	40.7×104	/ μl
Coagulation system		
PT	17.9	sec
APTT	41.5	sec
Fibrinogen	593	mg/ dl
FDP	10.5	μg/ dl
D-dimer	3.8	μg/ dl
Lupus anticoagulant	1.2	
Biochemistry		
TP	5.6	g/ dl
Alb	2.3	g/ dl
BUN	20	mg/ dl
Cr	1.04	mg/ dl
UA	3.6	mg/ dl
LDH	118	IU/ l
AST	26	IU/ l
ALT	13	IU/ l
ALP	386	IU/ l
γ- GTP	69	IU/ l
T-Bil	0.5	mg/ dl
Na	137	mEq/ l
K	4.7	mEq/ l
Cl	102	mEq/ l
Ca	4	mEq/ l
CK	29	IU/ l
Glu	121	mg/ dl
Fe	9	μg/ dl
UIBC	123	μg/ dl
Ferritin	377.2	ng/ ml
CRP	20.4	mg/ dl
KL-6	214	U/ ml

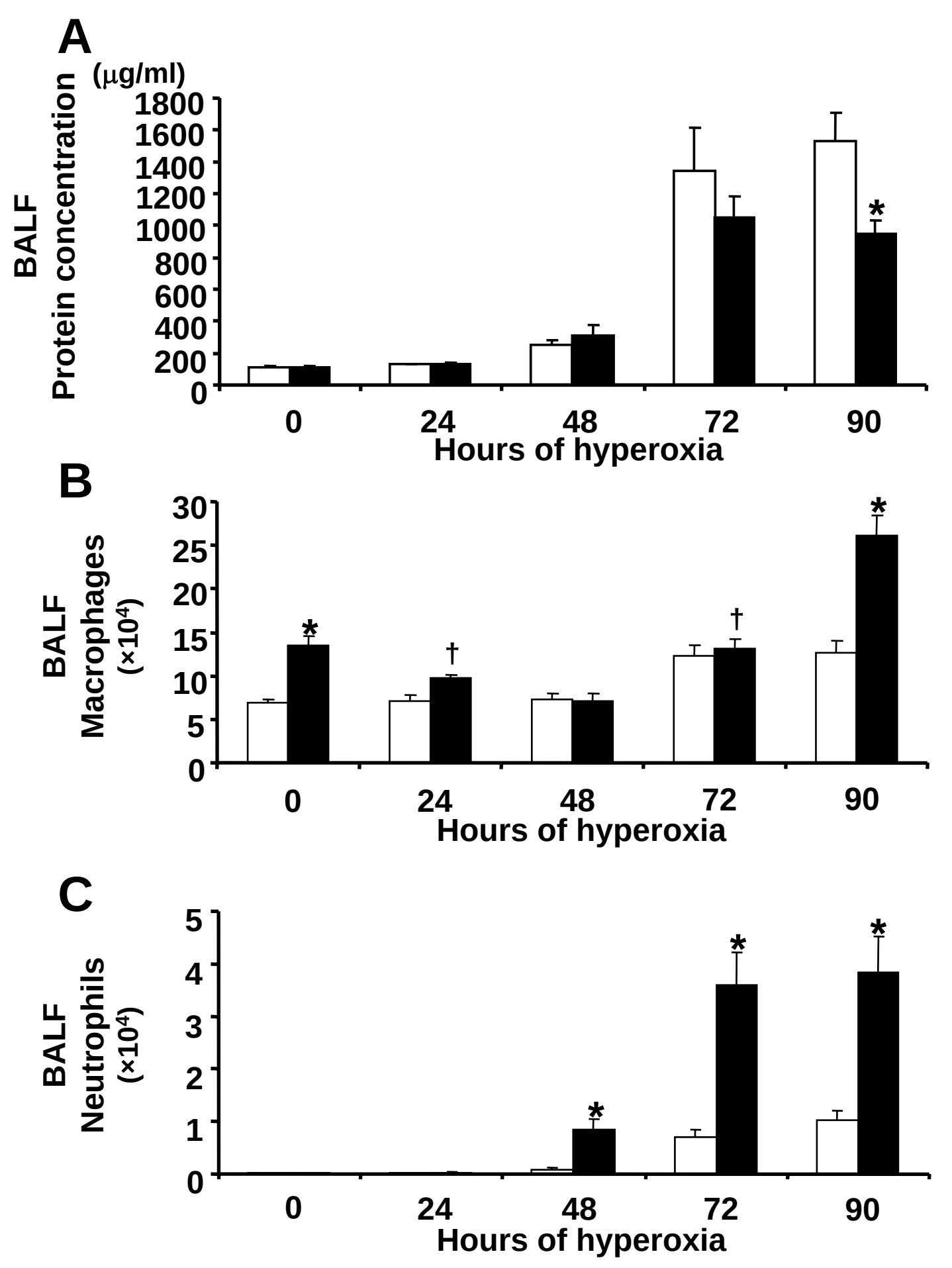
Serology

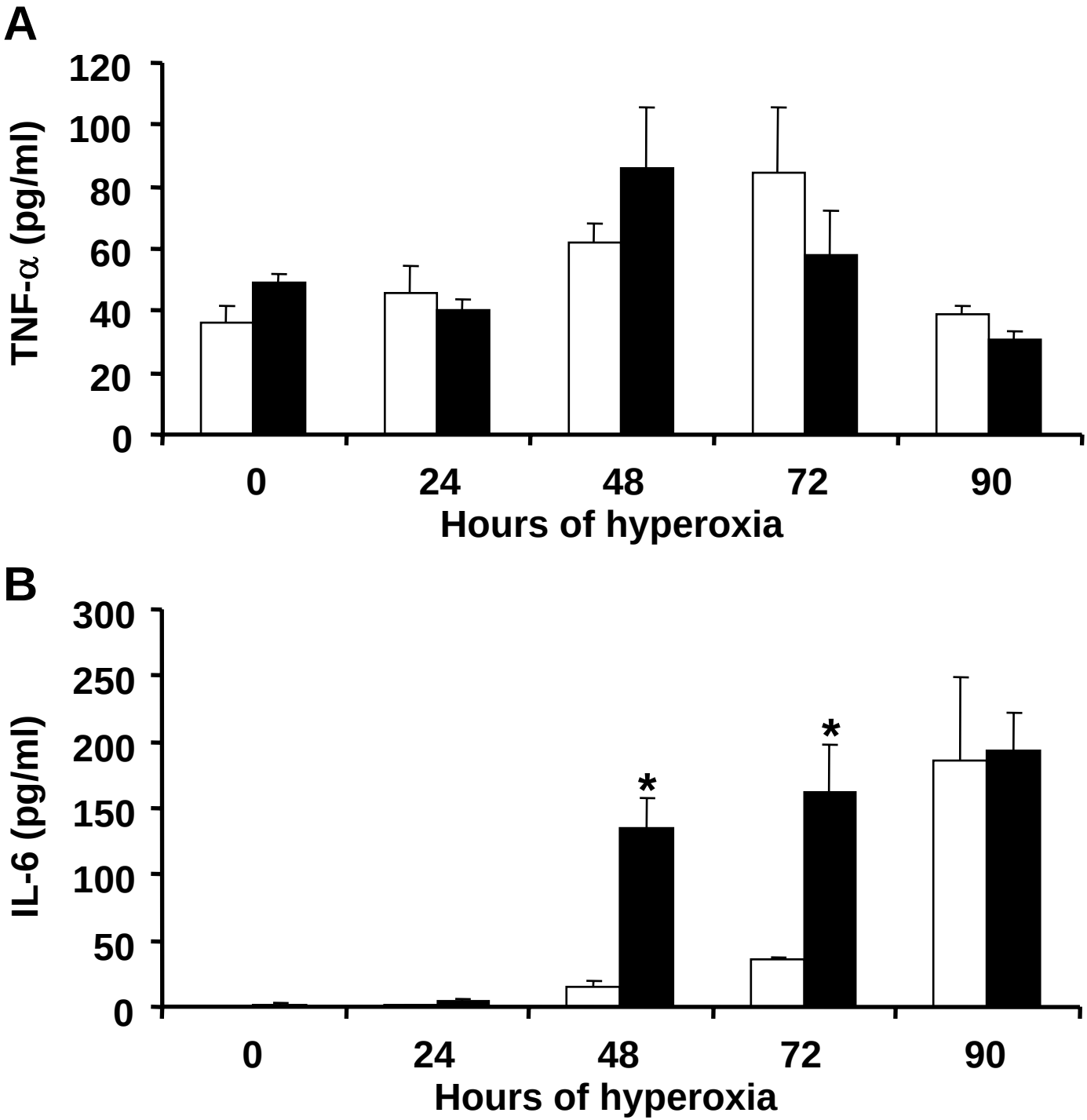
RF	270	U/ ml	β-D-glucan	< 3.95	pg/ ml
MMP-3	157	ng/ ml	HBs-Ag	(-)	
ANA	< x80		HBs-Ab	(-)	
CH50	52.1	U/ ml	HCV-Ab	(-)	
C3	96	mg/ dl	TPHA	(-)	
C4	12	mg/ dl			
MPO-ANCA	14.5	U/ ml			
PR3-ANCA	< 1.3	U/ ml	Blood culture	negative	
Anti CL-IgG	9.4	U/ ml			
Anti CL-β2GPI	< 1.3	U/ ml	Nerve conduction study	normal	

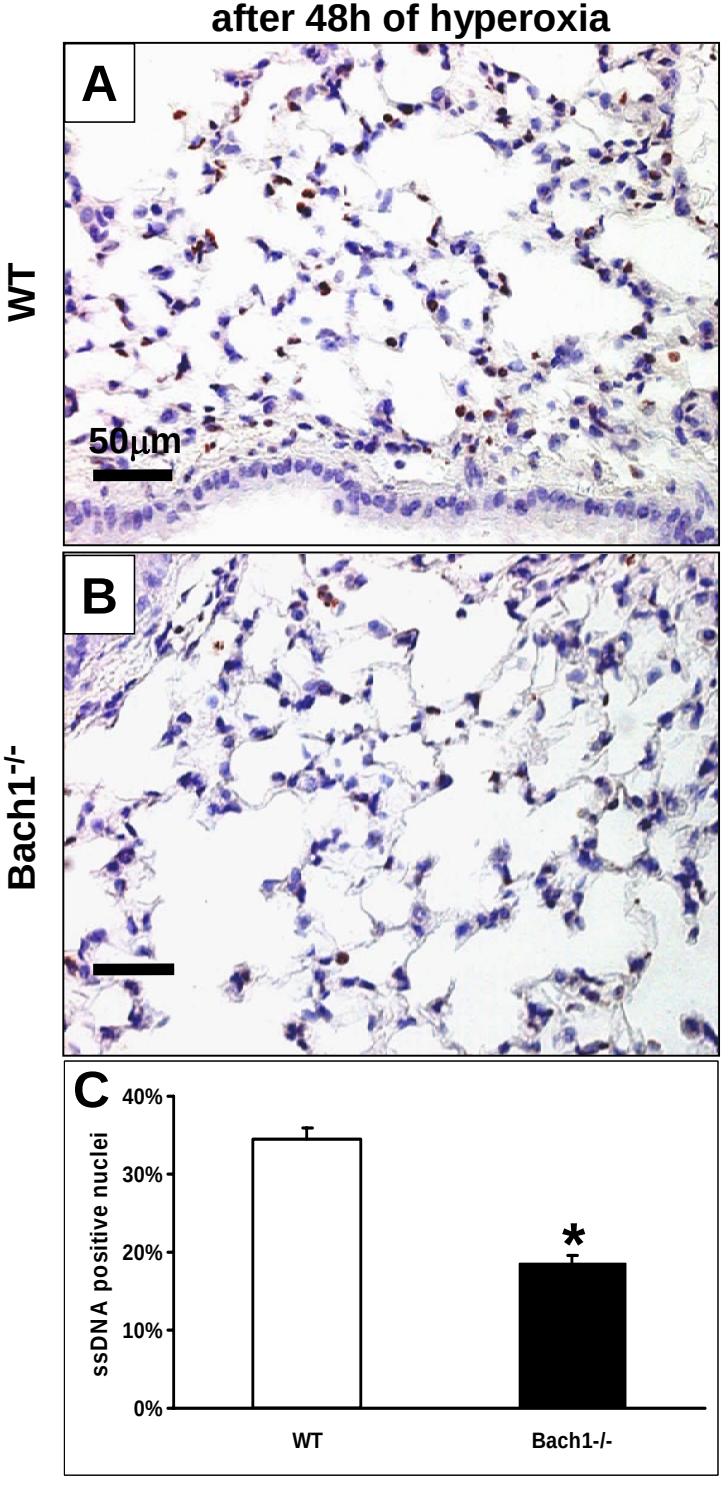

A
(ng/mg protein)
HO-1 protein level
45
40
35
30
25
20
15
10
5
0
*
*
*
*
*
0
24
48
72
90
Hours of hyperoxia
B
HO-2 expression level
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
0
48
90
Hours of hyperoxia

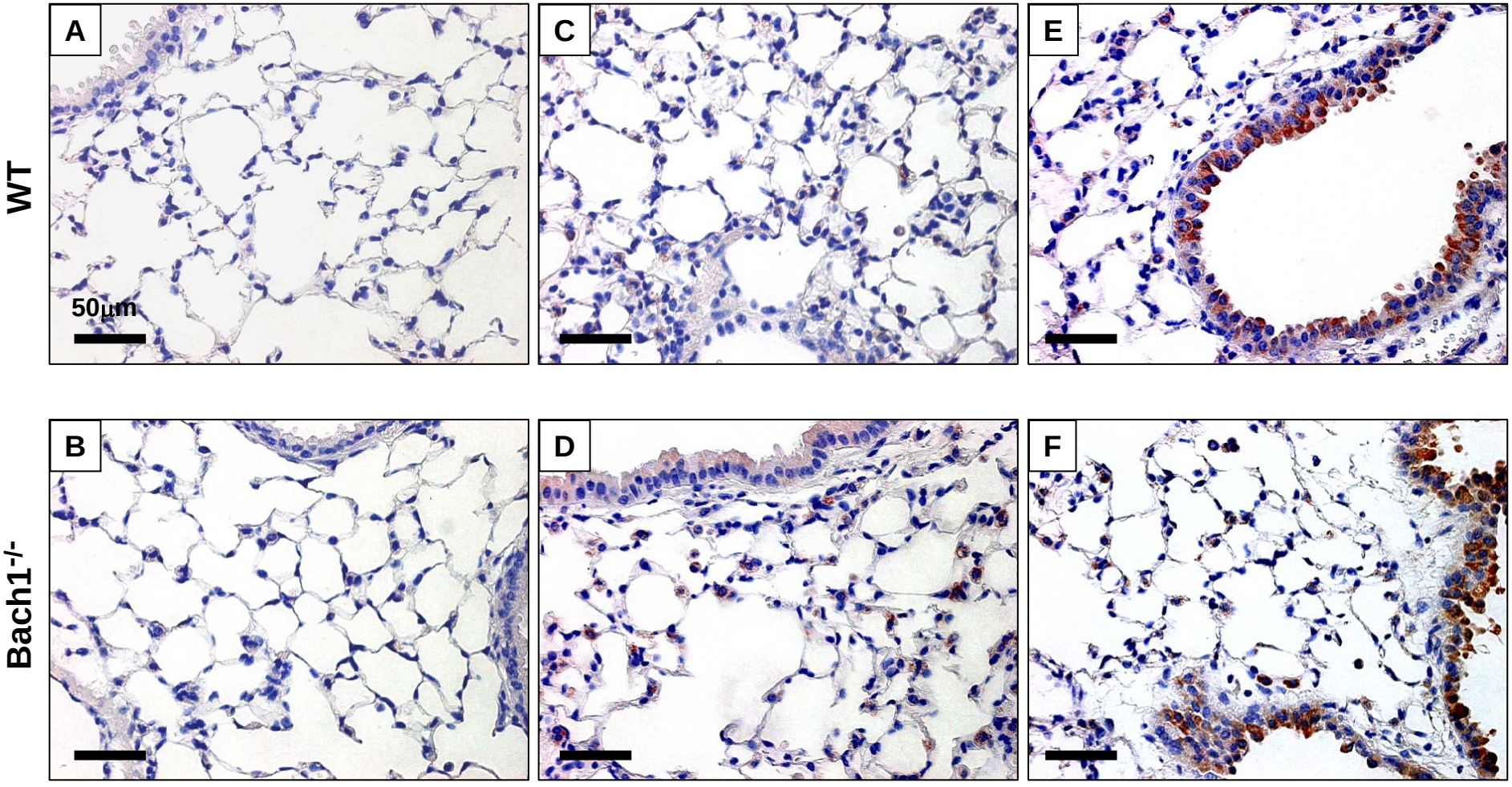

Percent Survival
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Hours of hyperoxia


A
C
E
B
D
F
WT
Bach1-/-
200μm
before hyperoxia
after 48h of hyperoxia
after 90h of hyperoxia

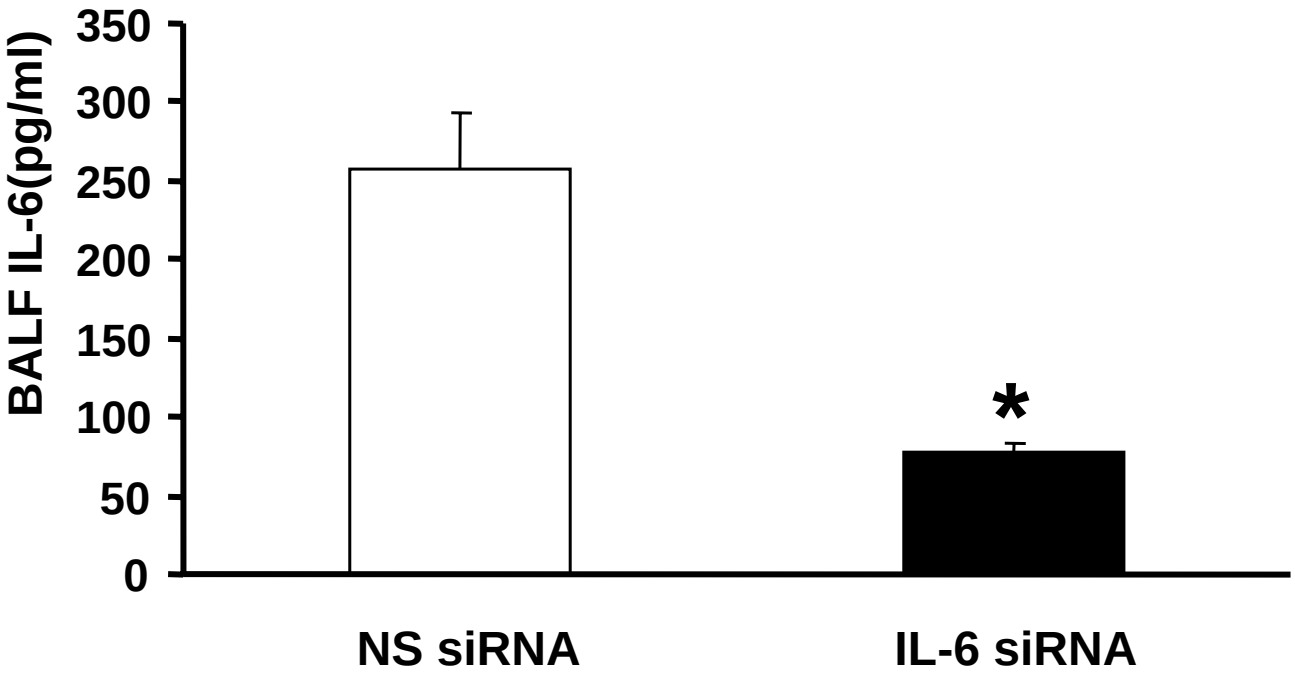

A
(μg/ml)
BALF
Protein concentration
1800
1600
1400
1200
1000
800
600
400
200
0
0
24
48
72
90
Hours of hyperoxia
*
B
BALF
Macrophages
(×10⁴)
30
25
20
15
10
5
0
*
†
†
*
0
24
48
72
90
Hours of hyperoxia
C
BALF
Neutrophils
(×10⁴)
5
4
3
2
1
0
*
*
*
0
24
48
72
90
Hours of hyperoxia


A
120
100
80
60
40
20
0
TNF-α (pg/ml)
0
24
48
72
90
Hours of hyperoxia
B
300
250
200
150
100
50
0
IL-6 (pg/ml)
*
*
0
24
48
72
90
Hours of hyperoxia

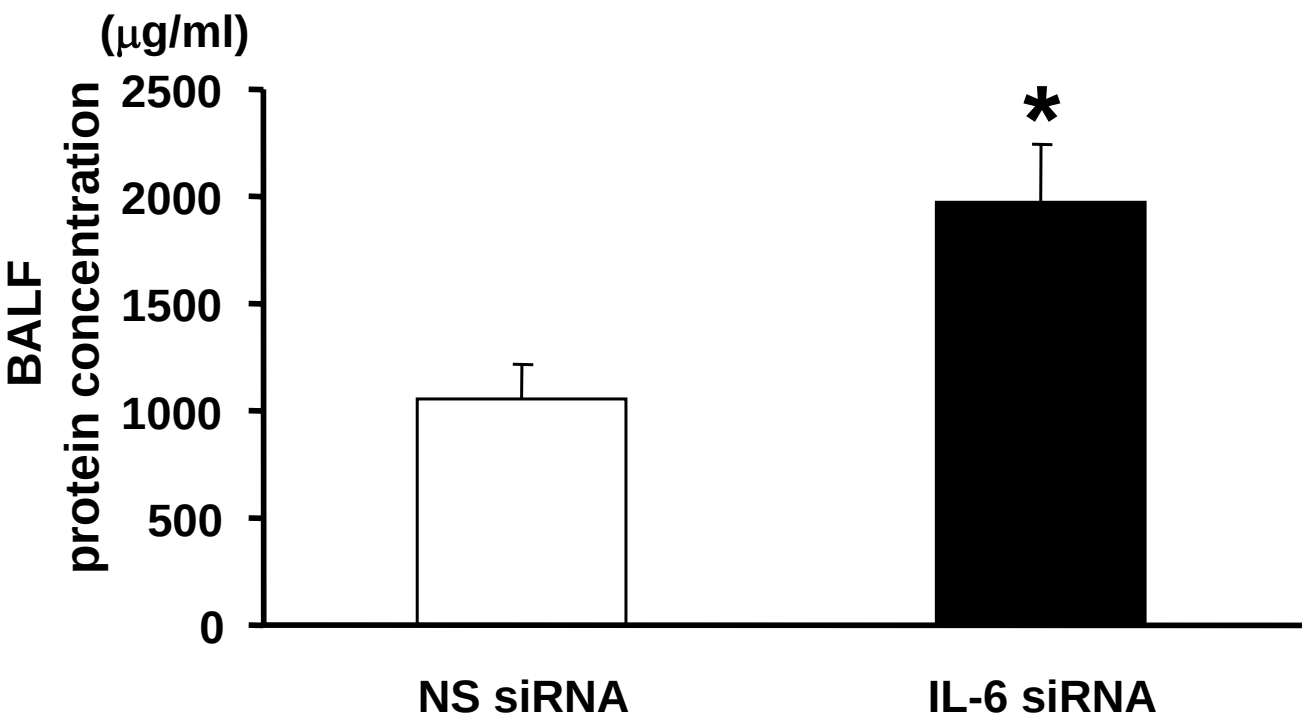

after 48h of hyperoxia
A
WT
50μm
B
Bach1-/-
C
ssDNA positive nuclei
40%
30%
20%
10%
0%
*
WT
Bach1-/-


A
C
E
B
D
F
WT
Bach1-/-
50µm
before hyperoxia
after 48h of hyperoxia
after 90h of hyperoxia

A


BALF IL-6(pg/ml)
350
300
250
200
150
100
50
0
*
NS siRNA
IL-6 siRNA

B


(μg/ml)
BALF
protein concentration
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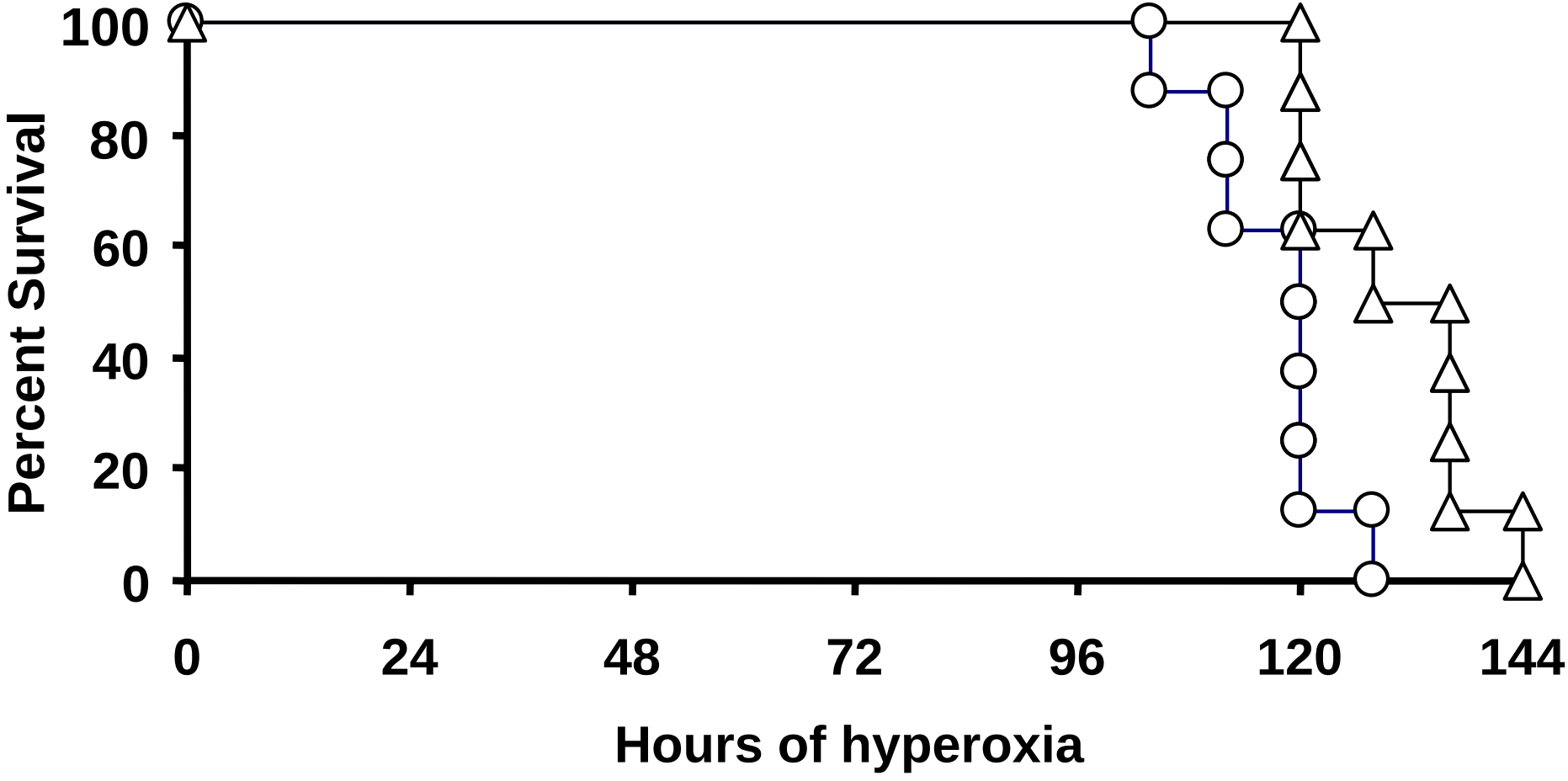
1500
1000
500
0
*
NS siRNA
IL-6 siRNA


Percent Survival
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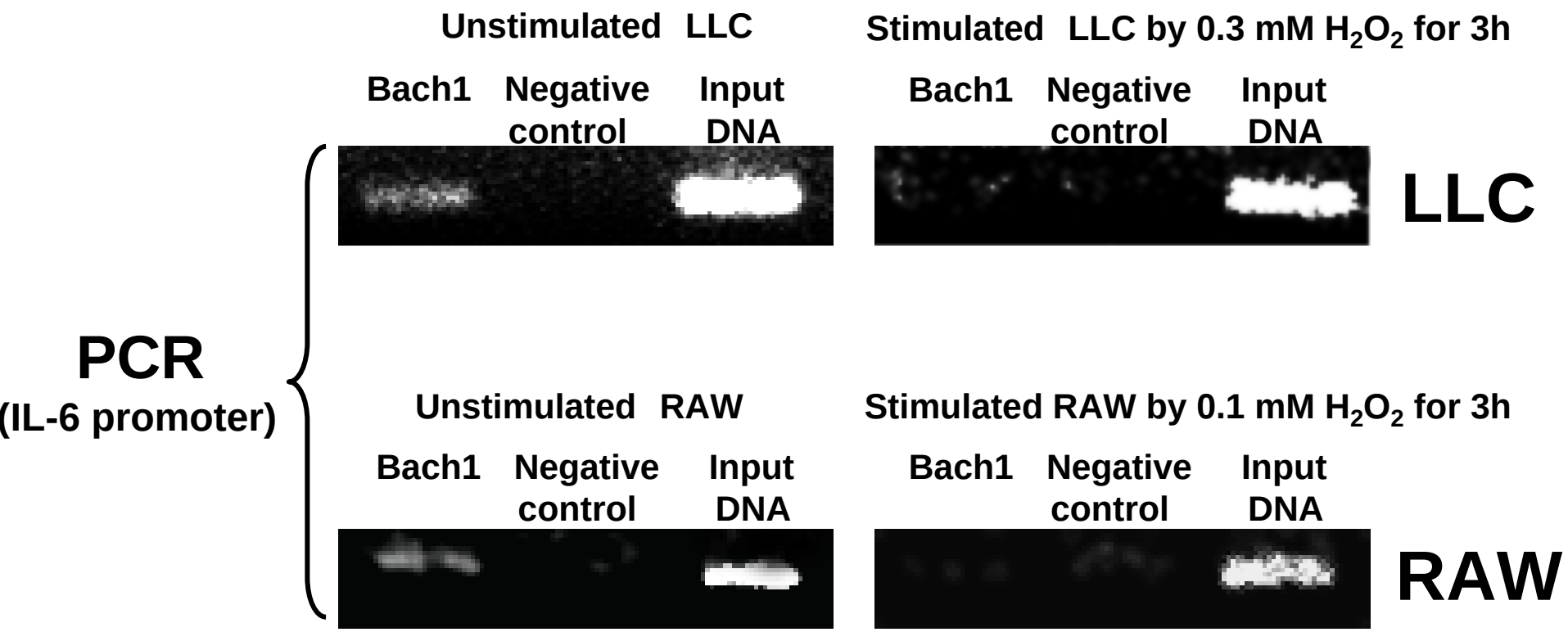
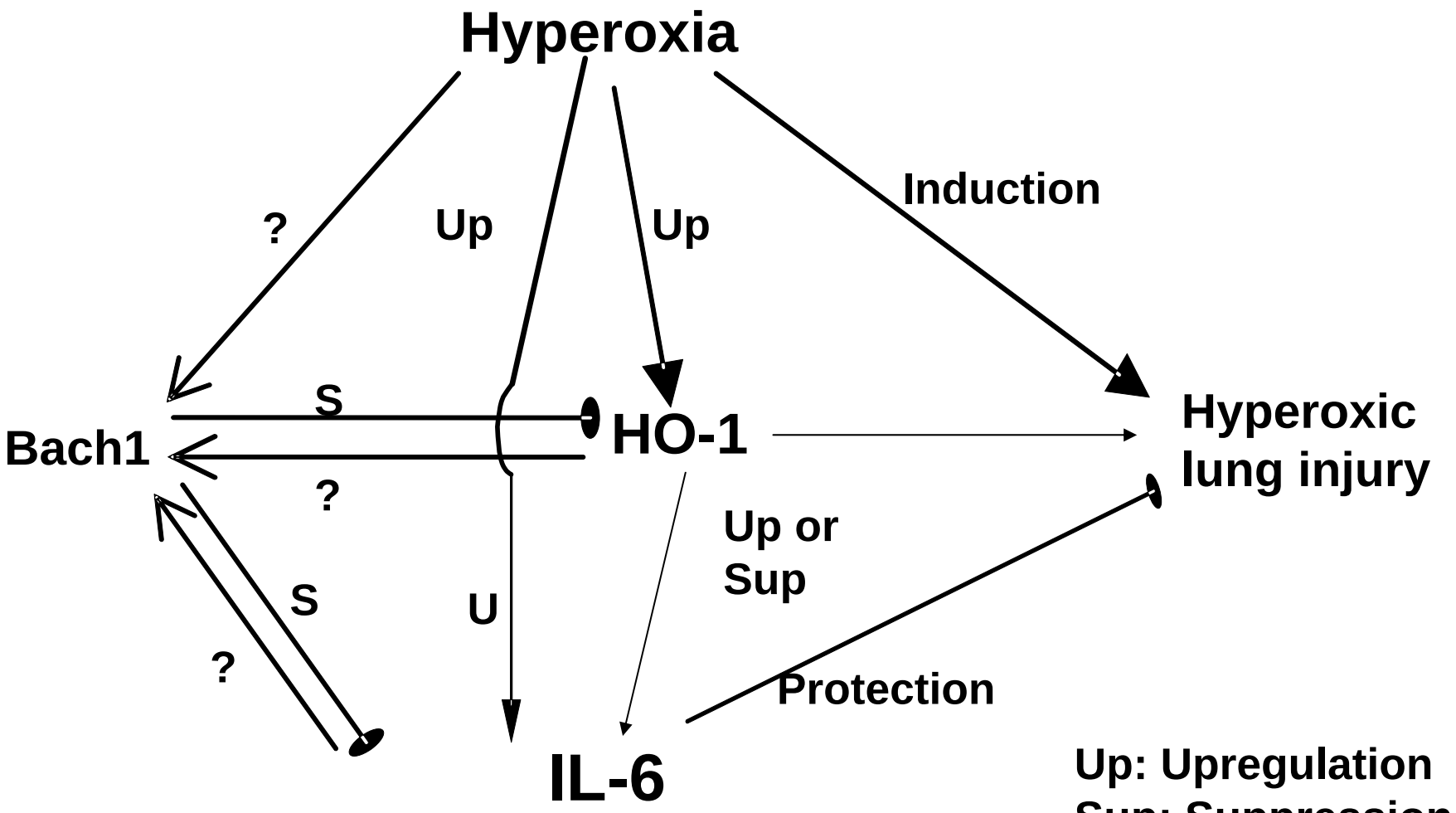
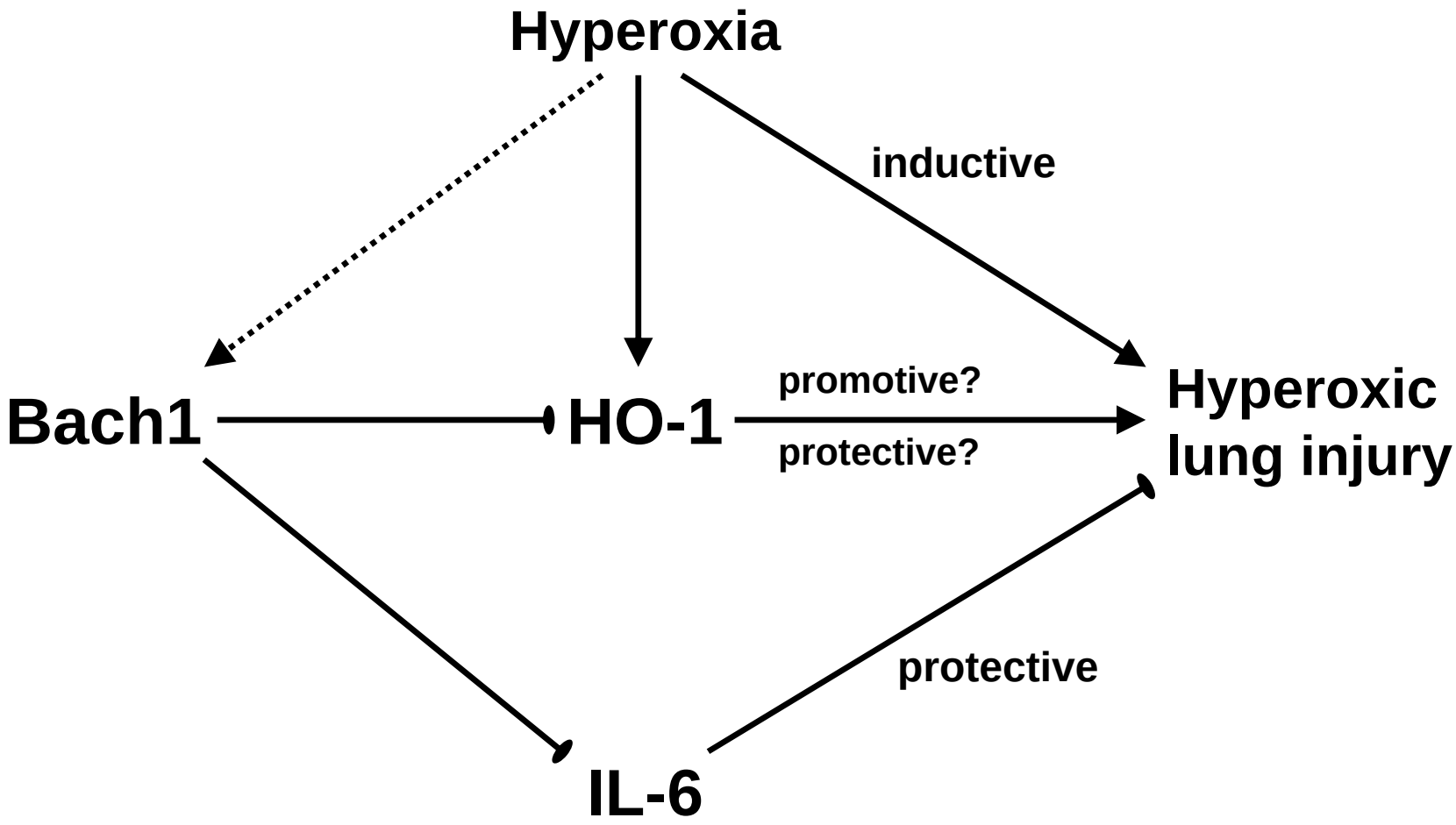
80
60
40
20
0
0
24
48
72
96
120
144
Hours of hyperoxia


Unstimulated LLC
Bach1
Negative control
Input DNA
Stimulated LLC by 0.3 mM H_2O_2 for 3h
Bach1
Negative control
Input DNA
LLC
PCR
(IL-6 promoter)
Unstimulated RAW
Bach1
Negative control
Input DNA
Stimulated RAW by 0.1 mM H_2O_2 for 3h
Bach1
Negative control
Input DNA
RAW


Hyperoxia
?
Up
Up
Induction
S
Bach1
HO-1
Hyperoxic
lung injury
?
Up or
Sup
S
U
?
Protection
IL-6
Up: Upregulation
Sup: Suppression


Hyperoxia
inductive
Bach1
HO-1
promotive?
protective?
Hyperoxic
lung injury
protective
IL-6