Supplementary Materials:

Supplementary Figures

Fig.S1

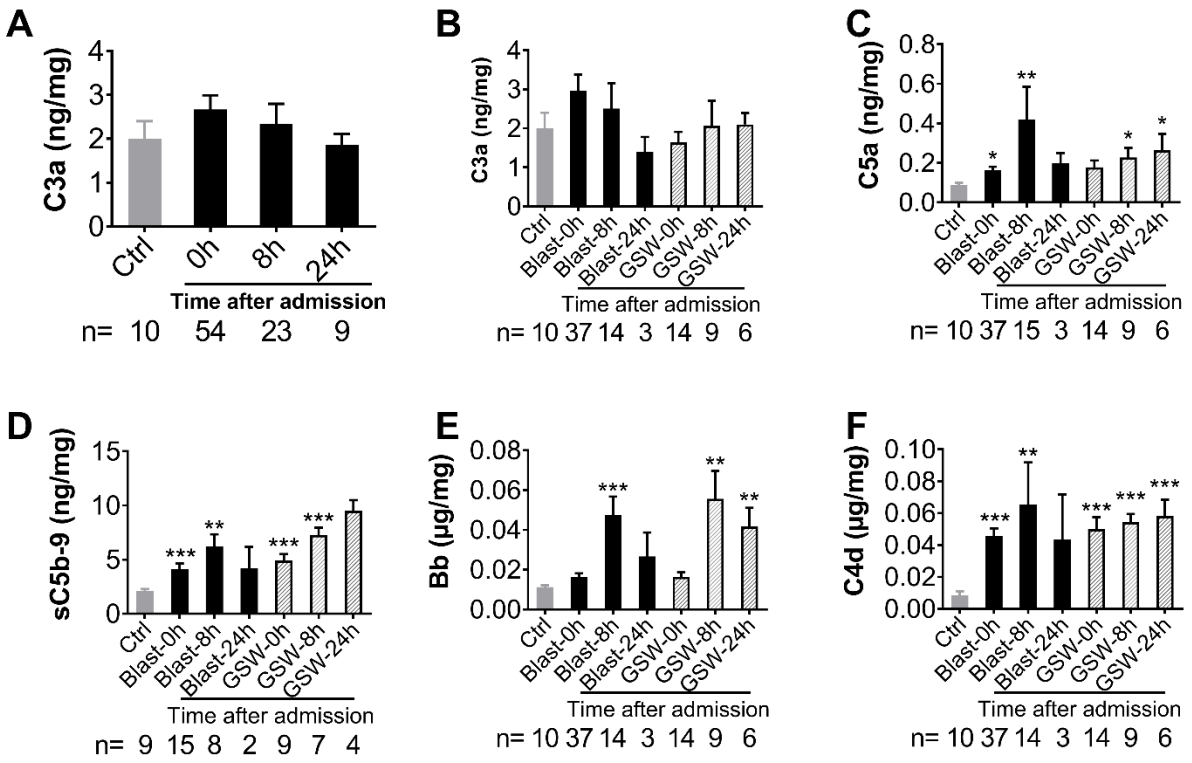

Fig. S1. Systemic activation of the complement pathways in battlefield trauma. **A-F**, plasma levels of complement factors (C3a, C5a, sC5b-9, Bb, and C4d) were measured by ELISA in healthy donors and trauma patients at admission to the hospital (0h), and at 8 and 24 hours after admission. **A**, plasma levels of C3a for all admitted patients; **B-F**, plasma levels of complement components in patients with two major mechanisms of injury - blast or gunshot wounds. The data are expressed as nanograms (C3a, C5a, C5b-9) or microgram (Bb, C4d) per milligram of total plasma proteins and presented as mean ± SEM, *= $p<0.05$, **= $p<0.01$, ***= $p<0.001$ *vs.* Healthy.

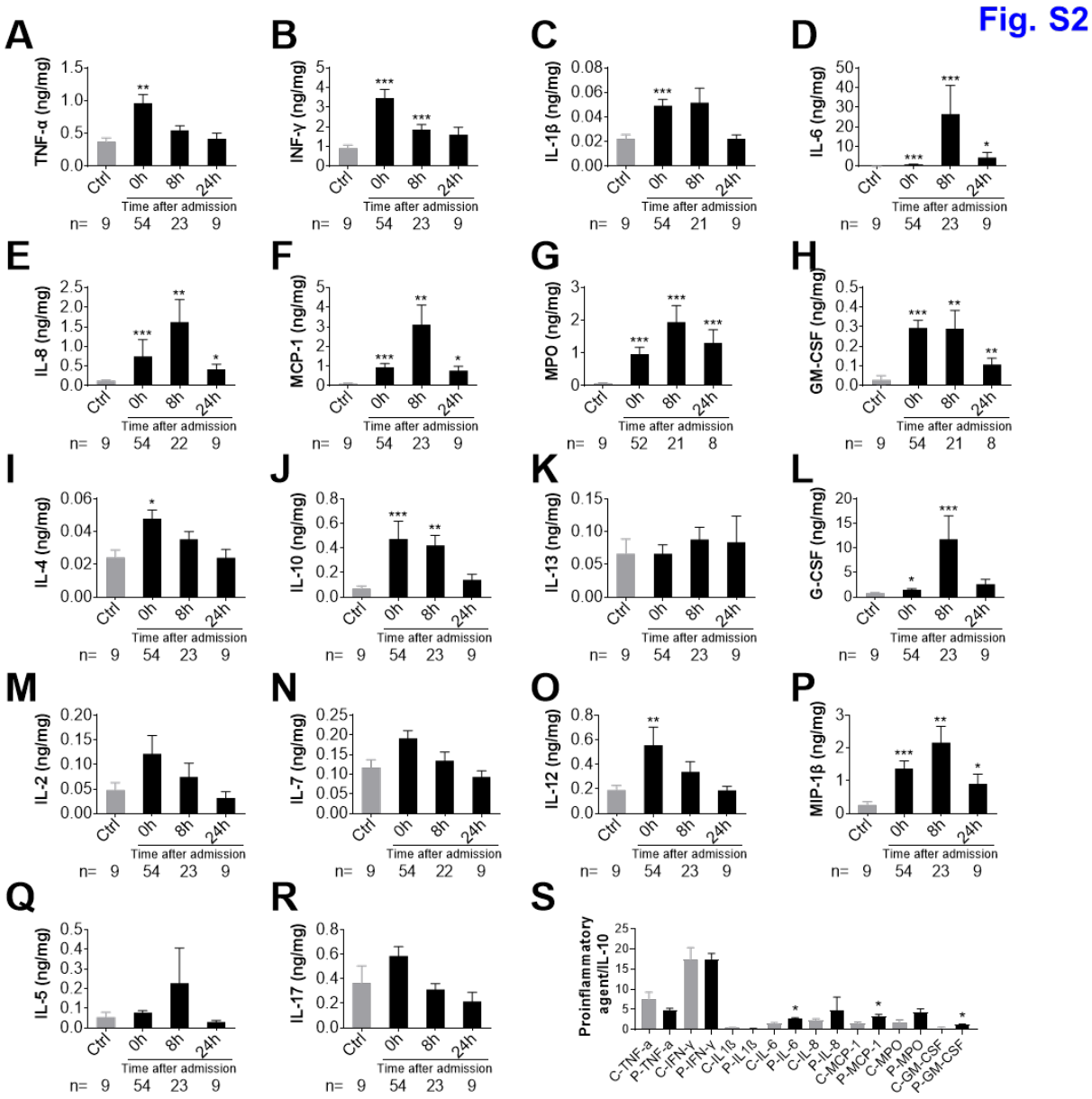

Fig. S2. Systemic inflammatory response to trauma. Inflammatory factors and cytokines were measured by ELISA and by Bio-Plex Kits, respectively. Pro-inflammatory factors/cytokines (**A-H**), anti-inflammatory cytokines (**I-L**), and regulatory cytokines (**M-R**) from healthy donors (n=10) and trauma patients on admission (n=54), and at 8 (n=23) and 24 hours (n=9) after admission were presented. The data are expressed as nanogram per milligram plasma protein and

presented as mean ± SEM, *= p<0.05, **=p<0.01, *** = p<0.001 vs. Healthy. Pro-inflammatory versus anti-inflammatory response (**S**). The ratio of systemic inflammatory factors (TNF-α, IFN-γ, IL-1β, IL-6, IL-8, MCP-1, MPO, and GM-CSF) to IL-10 on admission is given. C, Healthy controls (n=10); P, trauma patients (n=54). *= p < 0.05 vs. respective control (Unpaired t- test with Welch's correction).

Fig.S3

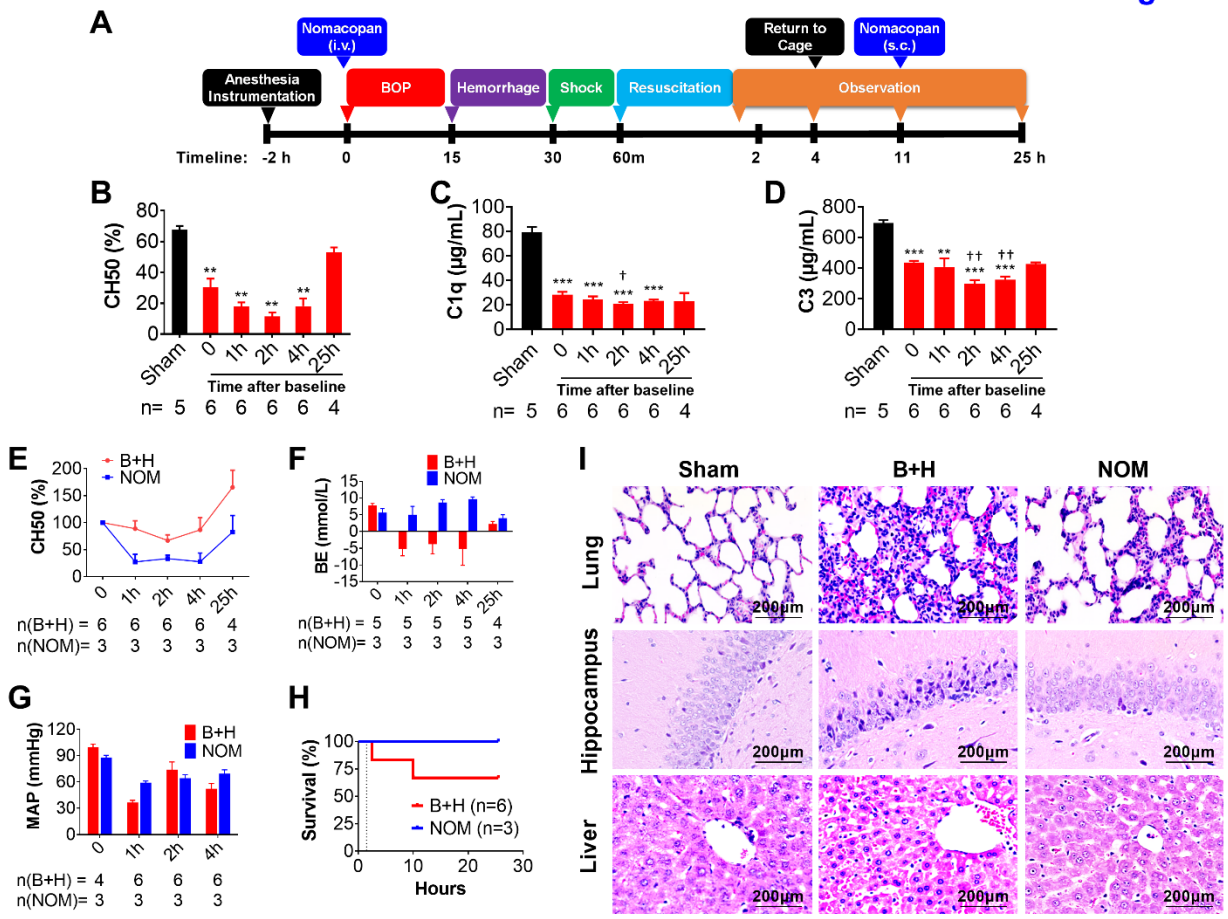

Fig. S3. Preventive effects of nomacopan treatment on the acidosis, hemodynamics, tissue damage, and survival after blast injury and hemorrhage in rats (Pilot study). (**A**) Experimental design. Anesthetized male rats were subjected to a moderate blast overpressure (BOP = 111.65 ± 2 kPa, t_+ = 3.16 ± 0.03 ms, impulse = 143 ± 2.26 kPa-ms) and a controlled hemorrhage (40% blood volume). After 30 min of shock, animals were resuscitated with Plasma-Lyte A (2× shed blood volume). Animals were randomized to three study arms: nomacopan (15 mg/kg, n=3), B + H (saline, n=6) and Sham (no injury, n=4). The first dose of nomacopan (7.5 mg/kg, i.v.) and a repeated dose of nomacopan (7.5 mg/kg, s.c.) were given immediately before blast injury and at 11 hours after blast injury, respectively. Blood pressure was monitored and

recorded with the BIOPAC MP160 Data Acquisition and Analysis Systems via the carotid arterial catheter. Blood and tissue samples were collected for blood complement/chemistry analysis and histopathological evaluation, respectively. (**B-D**) Bar graphs showing serum CH50, and plasma concentrations of C1q and C3, respectively. The data were presented as mean ± SEM, *= $p<0.05$, **= $p<0.01$, ***= $p<0.001$ *vs.* Sham, †= $p<0.05$, ††= $p<0.01$ *vs.* baseline (0 hour; by Mann-Whitney U test). (**E-G**) Bar graphs displaying the effect of nomacopan on CH50, BE, and MAP, respectively. The data were presented as mean ± SEM. (**H**) Effect of nomacopan treatment on survival. (**I**) Representative H & E images show the effect of nomacopan on histological changes of the organs. Labels: B+H = blast overpressure (BOP) + hemorrhage; NOM = nomacopan *i.v.* + BOP + hemorrhage + nomacopan *s.c.*; MAP = mean arterial pressure; BE= base excess/base deficit.

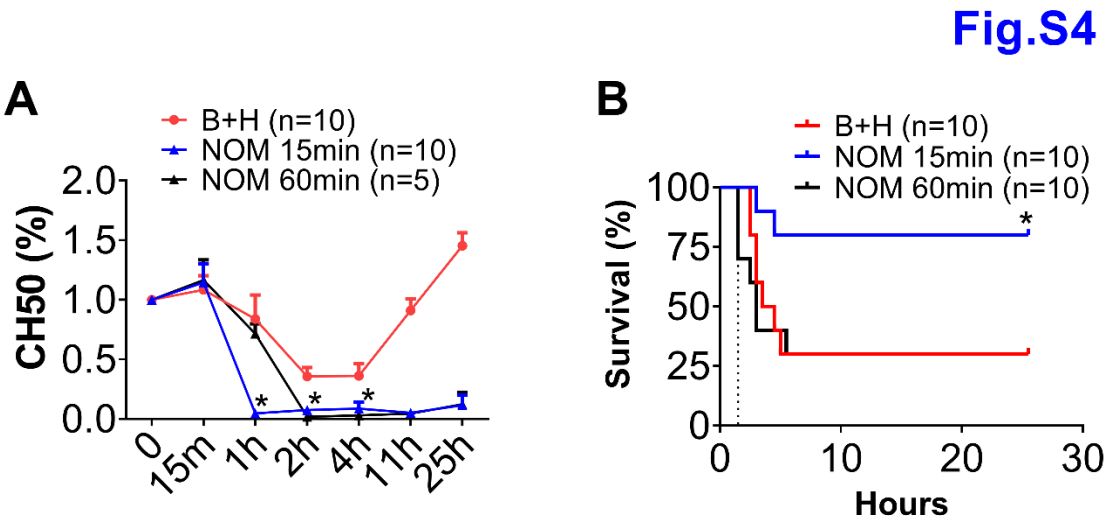

Fig. S4. Complement hemolytic activity and nomacopan effect on survival dependent on its administration time. Experimental groups: All animals were subjected to blast and hemorrhage, and treated with vehicle (saline, B+H group) or nomacopan**;** B + H = blast + hemorrhage; NOM = blast + nomacopan *i.v.* + hemorrhage + nomacopan *s.c.* in resuscitation phase; NOM-Late = nomacopan *i.v.,* with the first dose was infused at the end of hemorrhagic shock, immediately before fluid resuscitation + nopmacopan *s.c.* with the second dose was given in the resuscitation phase; *i.v.* = intravenous; *s.c.*= subcutaneous. **A**, the CH50 test data throughout the observation period; **B**, the survival distribution for three experimental groups was compared using the log-rank Mantel-Cox test; *= p <0.05. NOM, nomacopan.

Supplementary Tables

Table S1

	C3a		C5a		C5b-9		Bb		C4d	
	r	***p***	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***
Eotaxin	-0.13	0.76	0.18	0.70	0.16	0.73	-0.18	0.48	-0.03	0.89
FGF basic	-0.57	0.20	0.11	0.84	-0.07	0.91	-0.06	0.74	-0.27	0.53
G-CSF	-0.07	0.62	-0.09	0.52	-0.14	0.49	-0.11	0.43	-0.07	0.60
GM-CSF	0.13	0.35	0.09	0.50	-0.04	0.85	0.00	0.99	-0.22	0.12
IFN-γ	-0.09	0.51	-0.05	0.75	-0.10	0.64	-0.13	0.36	-0.25	0.07
IL-1β	0.05	0.71	-0.14	0.32	-0.25	0.22	-0.09	0.50	n/a	n/a
IL-1ra	0.54	0.24	-0.54	0.24	-0.04	0.96	-0.42	0.23	0.69	0.10
IL-2	0.07	0.62	0.06	0.67	-0.22	0.29	-0.09	0.54	-0.02	0.86
IL-4	-0.11	0.43	-0.04	0.80	-0.24	0.23	-0.17	0.21	-0.21	0.13
IL-5	-0.14	0.33	-0.01	0.96	-0.17	0.39	-0.09	0.51	**-0.27**	**0.05**
IL-6	**0.45**	**0.00**	n/a	n/a	n/a	n/a	n/a	n/a	0.17	0.23
IL-7	-0.12	0.37	-0.20	0.14	-0.22	0.28	-0.22	0.11	-0.25	0.06
IL-8	0.09	0.54	0.08	0.54	0.18	0.39	0.08	0.56	-0.09	0.51
IL-9	-0.43	0.35	0.07	0.91	0.00	>1.00	-0.06	0.74	-0.22	0.61
IL-10	**0.35**	**0.01**	**0.40**	**0.00**	0.34	0.09	**0.31**	**0.02**	0.00	0.97
IL-12	-0.23	0.09	-0.01	0.96	0.06	0.75	-0.15	0.29	-0.21	0.12
IL-13	0.08	0.57	0.10	0.48	-0.02	0.93	0.18	0.19	-0.26	0.06
IL-15	0.11	0.84	-0.18	0.71	0.04	0.96	-0.30	0.40	0.18	0.70
IL-17	-0.16	0.25	-0.05	0.70	-0.26	0.20	-0.16	0.25	n/a	n/a
IP-10	-0.25	0.59	0.36	0.44	0.18	0.71	-0.36	0.29	-0.27	0.53
MCP-1	**0.29**	**0.03**	n/a	n/a	n/a	n/a	n/a	n/a	-0.02	0.89
MPO	**0.34**	**0.01**	n/a	n/a	n/a	n/a	n/a	n/a	0.00	0.97
MIP-1α	-0.64	0.14	0.39	0.40	0.14	0.78	0.30	0.55	-0.45	0.29
MIP-1β	0.26	0.06	0.23	0.10	**0.52**	**0.01**	**0.29**	**0.03**	0.00	0.97
PDGF-bb	0.11	0.84	0.04	0.96	0.18	0.71	-0.42	0.23	0.36	0.42
RANTES	0.57	0.20	0.32	0.50	0.71	0.09	0.18	0.74	0.31	0.50
TNF-α	-0.06	0.66	-0.12	0.37	-0.23	0.25	-0.13	0.33	n/a	n/a
VEGF	-0.11	0.84	0.32	0.50	0.39	0.40	0.18	0.74	-0.11	0.79

Table S1. Correlations of complement and inflammatory mediators/cytokines/chemokines. Abbreviations: FGF basic, basic fibroblast growth factor; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; MCP-1, monocyte chemoattractant protein-1; MPO, myeloperoxidase; MIP, macrophage inflammatory protein; PDGF-bb, platelet-derived growth factor-BB; RANTES, regulated on activation, normal T cell expressed and secreted; VEGF, vascular endothelial growth factor. n/a, not applicable. The correlation analyses were performed by Spearman's rank correlation. A significant correlation (p<0.05) is indicated by boldface type.

Table S2

	Base Deficit		GCS		ISS		MAP		SIRS score		RBC		PLT units		FFP units		Crystalloids	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
C3a	-0.30	0.15	-0.26	0.06	**0.36**	**0.01**	-0.01	0.92	0.18	0.25	**0.31**	**0.03**	0.24	0.10	**0.37**	**0.01**	0.07	0.63
C5a	0.00	1.00	-0.24	0.09	**0.57**	**<0.001**	-0.23	0.09	0.14	0.36	**0.43**	**0.00**	0.24	0.09	0.26	0.06	**0.29**	**0.04**
C5b-9	-0.12	0.70	-0.25	0.22	0.32	0.12	-0.03	0.90	0.03	0.89	0.26	0.22	0.25	0.22	0.09	0.66	**0.43**	**0.03**
Bb	-0.16	0.45	-0.22	0.11	**0.41**	**0.00**	0.15	0.28	0.27	0.09	**0.49**	**0.00**	0.21	0.15	**0.41**	**0.00**	**0.35**	**0.01**
C4d	0.15	0.49	**-0.28**	**0.04**	-0.14	0.34	0.21	0.14	-0.04	0.80	**-0.29**	**0.04**	**-0.28**	**0.046**	**-0.35**	**0.01**	0.03	0.83
MPO	0.03	0.89	-0.19	0.20	**0.33**	**0.02**	-0.03	0.83	**0.37**	**0.02**	**0.47**	**0.00**	0.17	0.24	**0.36**	**0.01**	**0.35**	**0.01**
Eotaxin	-0.80	0.33	-0.45	0.10	-0.18	0.67	-0.27	0.53	-0.50	0.33	0.15	0.73	**-0.41**	**<0.001**	0.02	0.92	-0.40	0.36
FGF basic	-1.00	0.08	**-0.76**	**< 0.001**	0.21	0.66	-0.54	0.24	-0.11	0.83	0.67	0.12	**-0.61**	**<0.001**	0.58	0.19	-0.21	0.66
G-CSF	0.22	0.30	**-0.29**	**0.04**	**0.30**	**0.03**	-0.10	0.47	0.03	0.83	**0.29**	**0.04**	0.08	0.56	0.06	0.65	0.03	0.82
GM-CSF	0.35	0.09	**-0.48**	**0.00**	**0.28**	**0.04**	-0.23	0.09	0.01	0.95	**0.34**	**0.02**	0.10	0.46	**0.34**	**0.01**	-0.09	0.54
IFN-γ	0.29	0.16	**-0.28**	**0.05**	0.18	0.19	**-0.31**	**0.02**	-0.09	0.55	0.21	0.13	0.06	0.68	0.11	0.42	-0.07	0.62
IL-1β	0.36	0.08	**-0.39**	**0.00**	0.27	0.05	**-0.27**	**0.05**	-0.09	0.57	**0.39**	**0.00**	0.21	0.14	**0.27**	**0.05**	0.01	0.92
IL-1ra	-0.40	0.75	-0.27	0.29	-0.39	0.40	-0.61	0.17	0.63	0.50	0.16	0.73	**-0.61**	**<0.001**	0.58	0.19	-0.21	0.66
IL-2	-0.24	0.27	-0.09	0.55	0.15	0.29	-0.12	0.38	-0.01	0.96	0.14	0.34	-0.01	0.93	-0.07	0.60	0.10	0.50
IL-4	0.11	0.62	**-0.32**	**0.02**	0.27	0.05	**-0.35**	**0.01**	0.09	0.55	**0.32**	**0.02**	0.15	0.28	0.12	0.37	0.00	0.99
IL-5	0.20	0.36	**-0.33**	**0.02**	**0.30**	**0.03**	**-0.33**	**0.02**	0.03	0.85	**0.31**	**0.03**	0.14	0.32	0.11	0.45	-0.03	0.83
IL-6	0.25	0.25	-0.26	0.07	**0.35**	**0.01**	-0.03	0.83	0.20	0.20	**0.42**	**0.00**	0.12	0.37	**0.30**	**0.03**	**0.31**	**0.03**
IL-7	0.33	0.11	-0.26	0.06	0.21	0.13	**-0.38**	**0.00**	-0.05	0.73	0.20	0.17	0.15	0.29	0.06	0.66	-0.13	0.36
IL-8	0.21	0.33	**-0.36**	**0.01**	**0.41**	**0.00**	**-0.28**	**0.04**	0.18	0.25	**0.41**	**0.00**	0.20	0.15	0.25	0.07	0.11	0.46
IL-9	-1.00	0.08	**-0.76**	**< 0.001**	0.04	0.96	-0.50	0.27	0.11	>1.00	0.67	0.12	**-0.61**	**<0.001**	0.58	0.19	-0.25	0.59
IL-10	0.17	0.42	**-0.33**	**0.02**	**0.37**	**0.01**	-0.10	0.46	0.15	0.35	**0.43**	**0.00**	0.07	0.62	**0.30**	**0.03**	0.26	0.07
IL-12	0.28	0.18	-0.20	0.15	0.14	0.31	**-0.32**	**0.02**	-0.18	0.26	0.15	0.31	0.15	0.27	0.01	0.97	0.00	0.99
IL-13	0.01	0.97	**-0.32**	**0.02**	0.22	0.12	0.03	0.83	-0.09	0.59	**0.36**	**0.01**	0.13	0.35	0.24	0.08	0.18	0.21
IL-15	-1.00	0.08	-0.45	0.14	-0.43	0.35	-0.36	0.44	0.32	0.67	0.23	0.61	**-0.61**	**<0.001**	0.32	0.49	-0.43	0.35
IL-17	0.08	0.69	**-0.38**	**0.01**	**0.33**	**0.02**	**-0.40**	**0.00**	0.12	0.44	**0.36**	**0.01**	0.14	0.30	0.17	0.22	0.07	0.64
IP-10	-0.80	0.33	**-0.67**	**< 0.001**	0.21	0.66	-0.39	0.40	-0.74	0.17	0.22	0.64	**-0.41**	**<0.001**	0.22	0.63	-0.64	0.14
MCP-1	0.22	0.31	**-0.33**	**0.02**	**0.40**	**0.00**	-0.16	0.24	0.05	0.74	**0.45**	**0.00**	0.24	0.08	**0.43**	**0.00**	0.18	0.21
MIP-1α	-0.80	0.33	**-0.76**	**< 0.001**	0.50	0.27	-0.46	0.30	0.21	0.83	**0.85**	**0.03**	**-0.20**	**<0.001**	0.58	0.19	0.14	0.78
MIP-1β	0.35	0.09	-0.22	0.12	0.18	0.21	-0.19	0.16	-0.02	0.91	**0.29**	**0.04**	0.14	0.31	**0.36**	**0.01**	0.20	0.17
PDGF-bb	-0.80	0.33	**-0.58**	**0.05**	-0.04	0.96	-0.71	0.09	-0.74	0.17	0.18	0.70	**-0.61**	**<0.001**	0.30	0.52	-0.43	0.35
RANTES	0.40	0.75	-0.27	0.29	-0.32	0.50	-0.21	0.66	0.32	0.67	0.18	0.70	0.20	0.57	-0.02	0.88	0.07	0.91
TNF-α	0.27	0.20	**-0.31**	**0.03**	0.21	0.13	**-0.28**	**0.04**	-0.07	0.67	**0.29**	**0.04**	0.11	0.41	0.14	0.32	0.00	0.99
VEGF	-0.80	0.33	-0.58	0.05	-0.18	0.71	-0.29	0.56	-0.21	0.67	0.50	0.25	**-0.20**	**<0.001**	0.19	0.70	-0.07	0.91

Table S2. Table S2. Correlations between complement/inflammatory cytokines/chemokines and clinical outcomes. Abbreviations: MPO, myeloperoxidase; FGF basic, basic fibroblast growth factor; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor. MCP-1, monocyte chemoattractant protein-1 (also known as CCL2); MIP, macrophage inflammatory protein (also known as CCL3); PDGF-bb, platelet-derived growth factor-BB; RANTES, regulated on activation, normal T cell expressed and Secreted (also known as CCL5); VEGF, vascular endothelial growth factor. n/a, not applicable. The correlation analyses were performed by Spearman's rank correlation. A significant correlation ($p<0.05$) is indicated by boldface type.

Table S3

	Reference			Overpressure			Reflected		
	P0 (kPa)	t+ (ms)	I (kPa-ms)	P0 (kPa)	t+ (ms)	I (kPa-ms)	P0 (kPa)	t+ (ms)	I (kPa-ms)
Pilot study									
B+H (n=6)	101.20 ± 1.13	3.31 ± 0.03	136.37 ± 1.11	108.49 ± 1.22	3.29 ± 0.03	137.46 ± 1.12	153.13 ± 2.45	3.45 ± 0.01	171.17 ± 1.64
NOM_0' (n=3)	111.70 ± 0.65	3.33 ± 0.02	144.13 ± 0.65	119.75 ± 0.70	3.31 ± 0.02	145.29 ± 0.65	166.37 ± 5.00	3.48 ± 0.01	180.37 ± 0.95
Main study									
B+H (n=10)	108.93 ± 1.22	3.32 ± 0.01	140.23 ± 0.77	116.78 ± 1.31	3.30 ± 0.01	141.35± 0.78	161.17 ± 1.87	3.48 ± 0.03	178.51 ± 1.21
NOM_15' (n=10)	107.96 ± 1.11	3.27 ± 0.02	140.54 ± 0.70	115.74 ± 1.19	3.25 ± 0.02	141.67 ± 0.70	162.84 ± 1.36	3.49 ± 0.03	178.82 ± 1.07
NOM_60' (n=10)	108.47 ± 1.01	3.30 ± 0.03	141.00 ± 0.55	116.29 ± 1.09	3.28 ± 0.03	142.13 ± 0.56	158.48 ± 2.16	3.49 ± 0.03	178.34 ± 1.07

Table S3. Blast wave parameters from pilot and main (treatment) studies. Legend: B + H group = blast + hemorrhage; NOM group = nomacopan *i.v.* + blast + hemorrhage + nomacopan *s.c.*; P0 (peak pressure) in kPa (the kilopascal, a unit of pressure); t+ [the positive-pressure phase duration in milliseconds (ms)]; I [impulse (kPa-ms)].

Table S4

Parameters		0	15mim	1h	4h	11h	25hs/EOS
Arterial pH	B+H (n=10)	7.44 ± 0.02	7.25 ± 0.07#	7.30 ± 0.16#	7.07 ± 0.37#	7.44 ± 0.06	7.40 ± 0.03
	nomacopan (n=10)	7.44 ± 0.03	7.33 ± 0.08#	7.38 ± 0.16	7.41 ± 0.16*	7.44 ± 0.10	7.47 ± 0.09
Arterial pCO2 (mmHg)	B+H (n=10)	51.56 ± 4.49	79.16 ± 14.07#	51.71 ± 17.51	68.24 ± 24.35	54.17 ± 7.54	50.30 ± 8.90
	nomacopan (n=10)	51.06 ± 4.20	64.75 ± 10.90#*	46.82 ± 18.49#	50.00 ± 12.21	52.06 ± 6.27	40.64 ± 8.56#
Arterial HCO3 (mmHg)	B+H (n=10)	34.72 ± 2.00	34.57 ± 1.89	23.30 ± 5.55#	32.25 ± 7.26	36.27 ± 0.60	24.98 ± 8.65#
	nomacopan (n=10)	34.59 ± 1.32	34.07 ± 1.34	26.10 ± 2.28#	31.13 ± 5.09#	33.45 ± 2.46	28.88 ± 2.43#
Chloride (mmol/L)	B+H (n=10)	100.20 ± 1.32	100.70 ± 1.34	103.60 ± 2.59#	104.38 ± 3.07#	103.00 ± 4.69	103.00 ± 2.65
	nomacopan (n=10)	101.56 ± 1.67	99.78 ± 1.86	101.38 ± 3.54	102.67 ± 2.40	101.57 ± 2.51	105.71 ± 2.36#
iCa (mmol/L)	B+H (n=10)	1.37 ± 0.03	1.44 ± 0.05#	1.35 ± 0.04	1.25 ± 0.10#	1.34 ± 0.02	1.38 ± 0.07
	nomacopan (n=10)	1.35 ± 0.04	1.42 ± 0.06#	1.35 ± 0.05	1.29 ± 0.05#	1.34 ± 0.05	1.37 ± 0.05
Glucose (mg/dL)	B+H (n=10)	188.10 ± 20.95	269.00 ± 50.14#	375.56 ± 98.61#	131.71 ± 93.87	157.00 ± 6.08	250.33 ± 41.49
	nomacopan (n=10)	180.00 ± 27.87	263.80 ± 51.39#	366.88 ± 127.97#	170.44 ± 52.22	147.75 ± 19.00#	153.38 ± 24.33#*

Table S4. Blood chemistry changes in control and nomacopan treatment (NOM_15') groups.

Legend: Data are expressed as mean ±SD; statistical analyses were performed by Mann-Whitney U test; *=p <0.05 vs. the vehicle (saline); #=p <0.05 vs. baseline (0 hours).