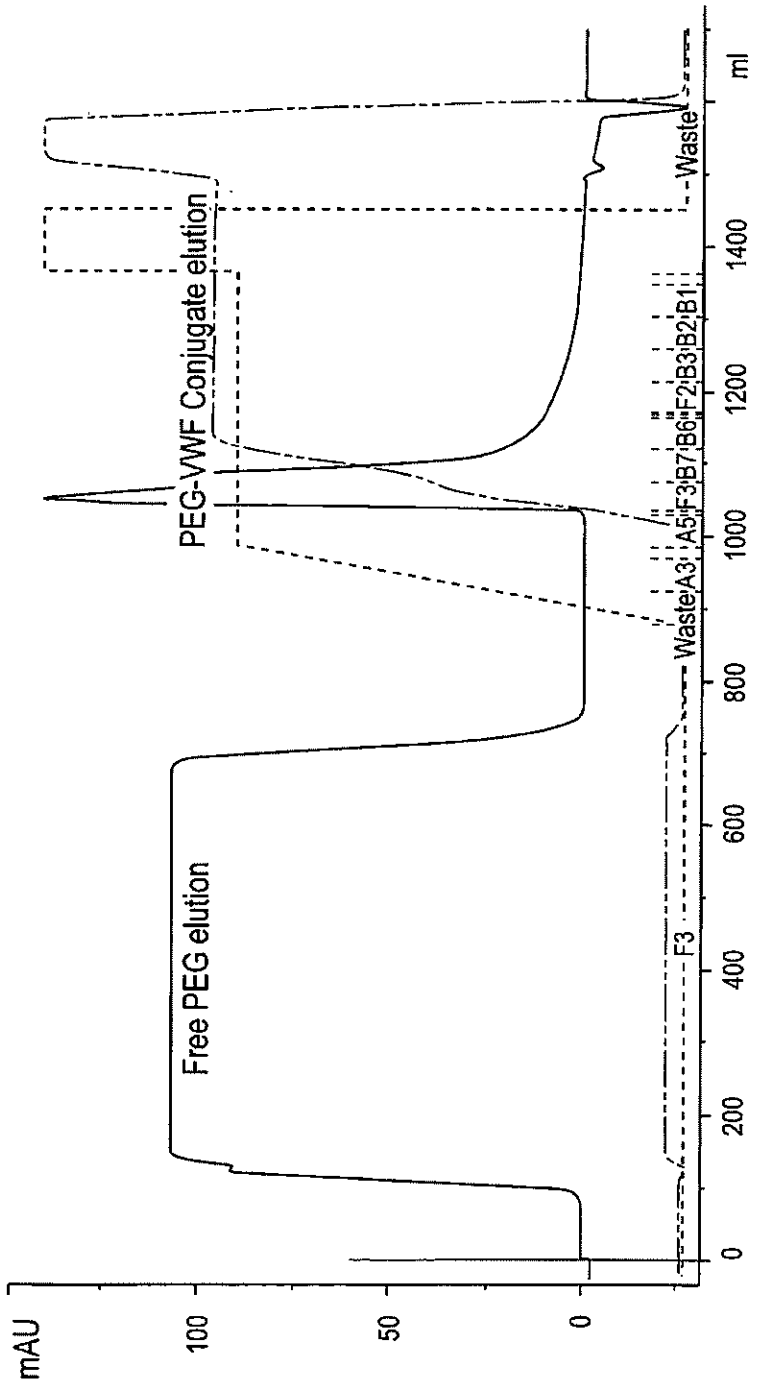

mAU
100
50
0
0
200
400
600
800
1000
1200
1400
ml
Free PEG elution
PEG-VWF Conjugate elution
Waste
F3
Waste
A3
A5
F3
B6
B7
F2
B3
B2
B1

Figure 1

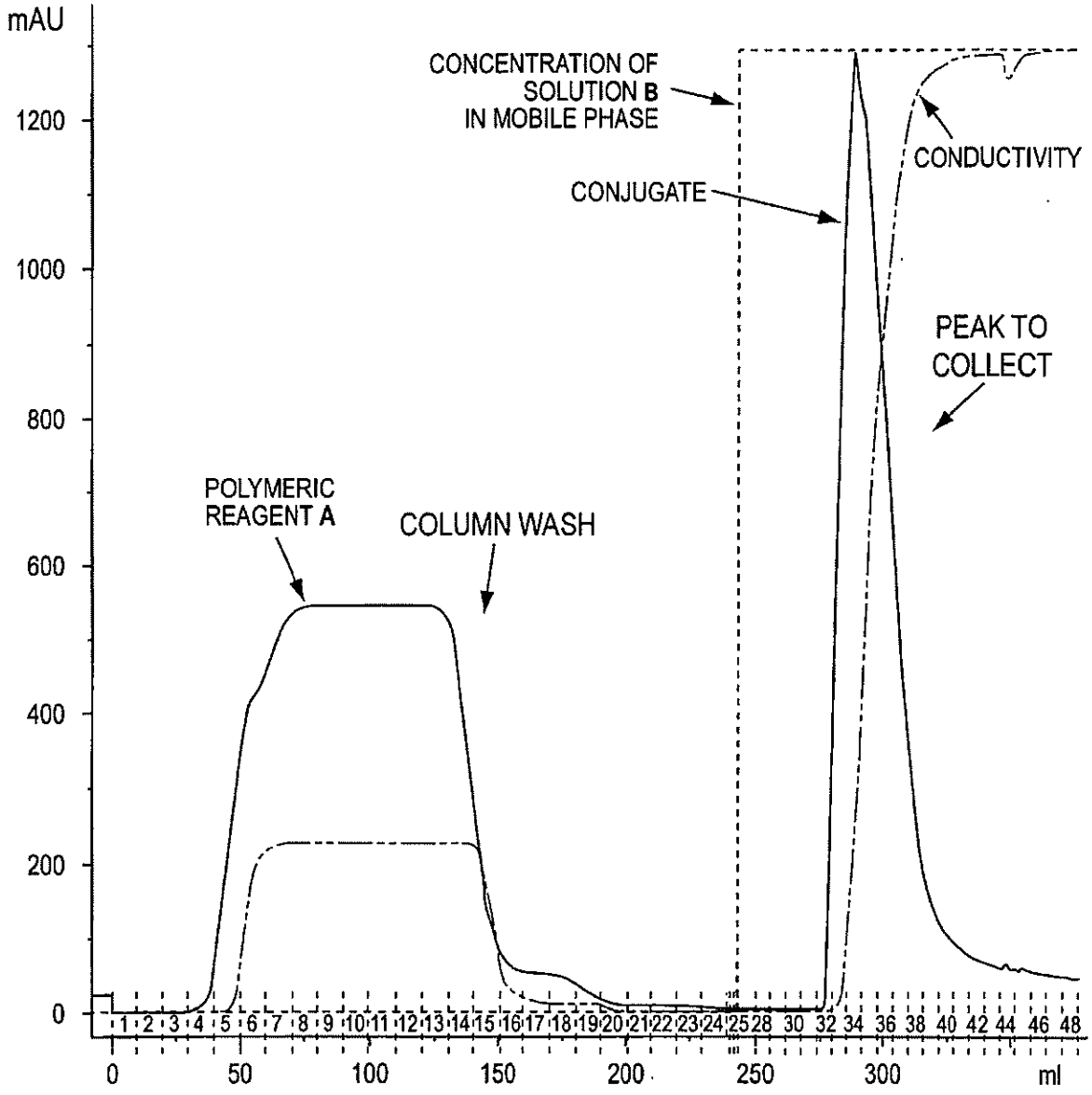

mAU
1200
1000
800
600
400
200
0
CONCENTRATION OF SOLUTION B IN MOBILE PHASE
CONJUGATE
CONDUCTIVITY
PEAK TO COLLECT
POLYMERIC REAGENT A
COLUMN WASH
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 28 30 32 34 36 38 40 42 44 46 48
0 50 100 150 200 250 300 ml

Figure 2A

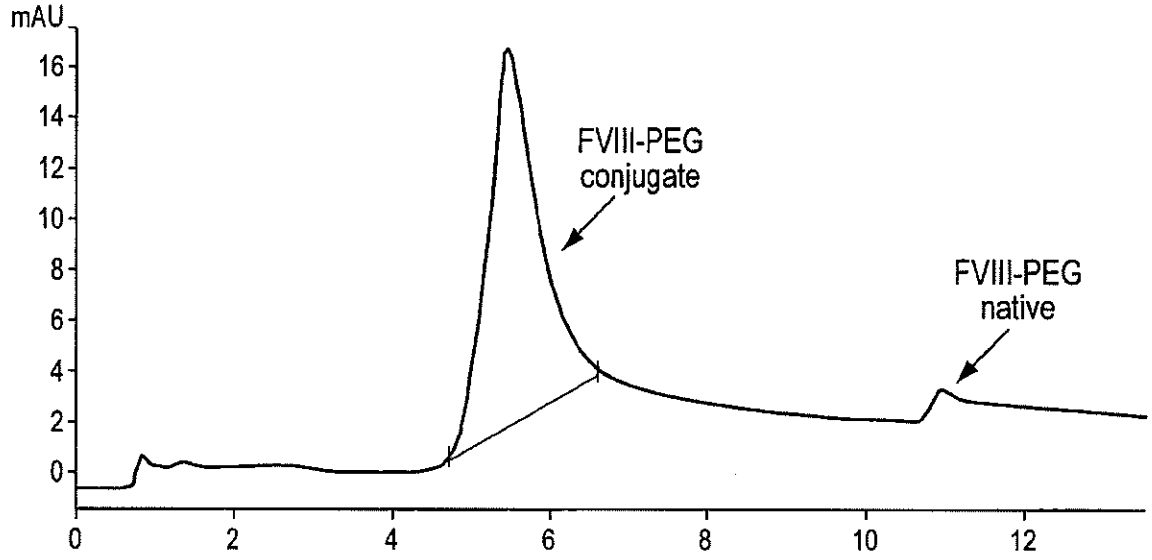


Figure 2B

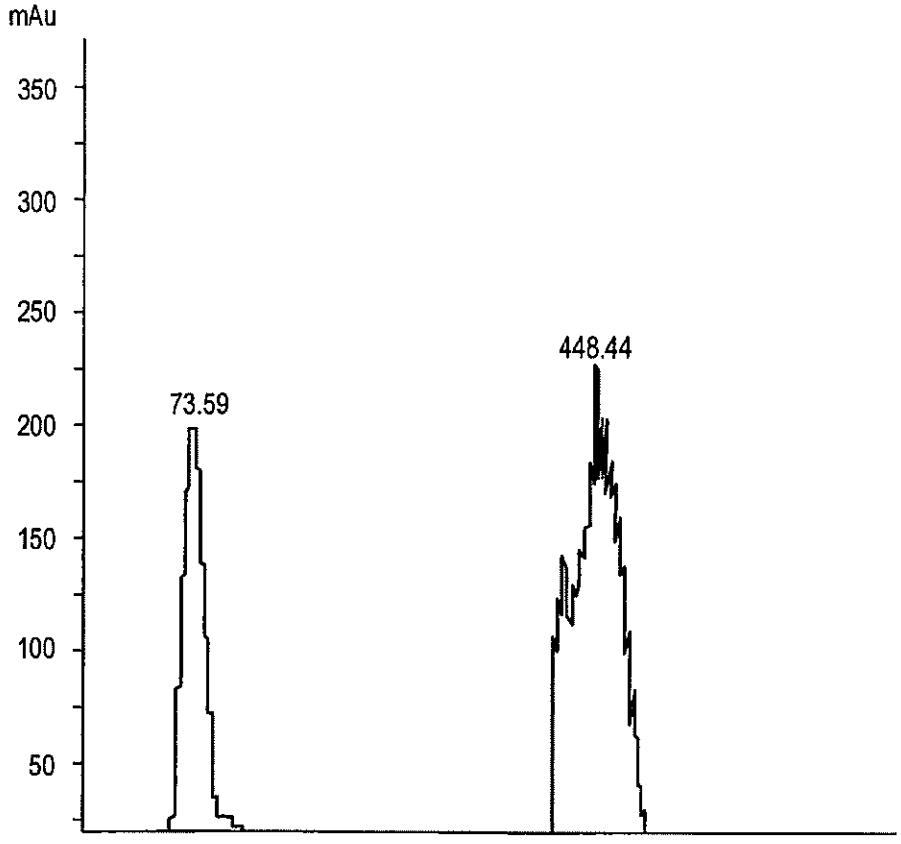


Figure 3A

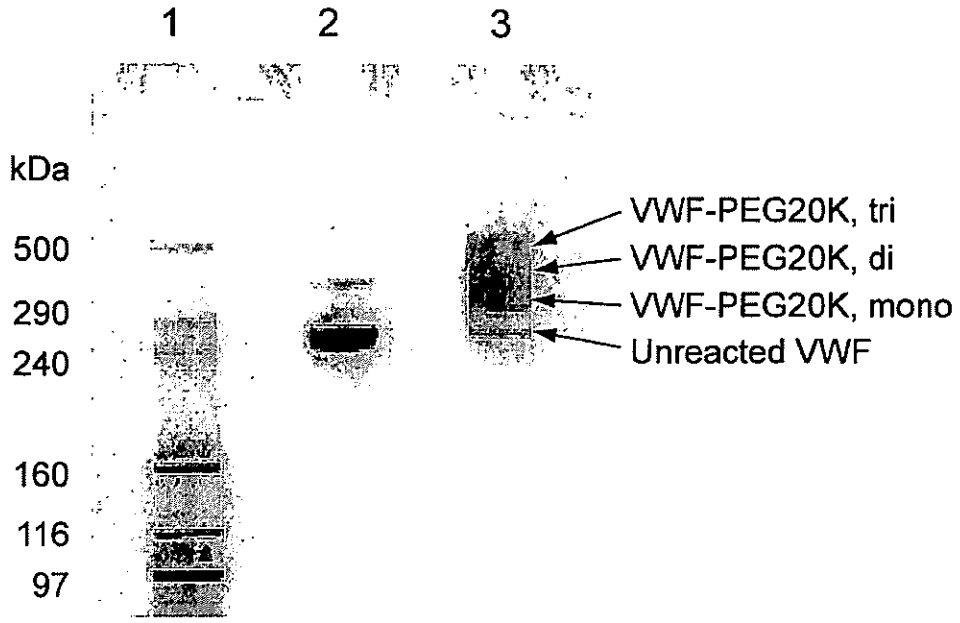


Figure 3B

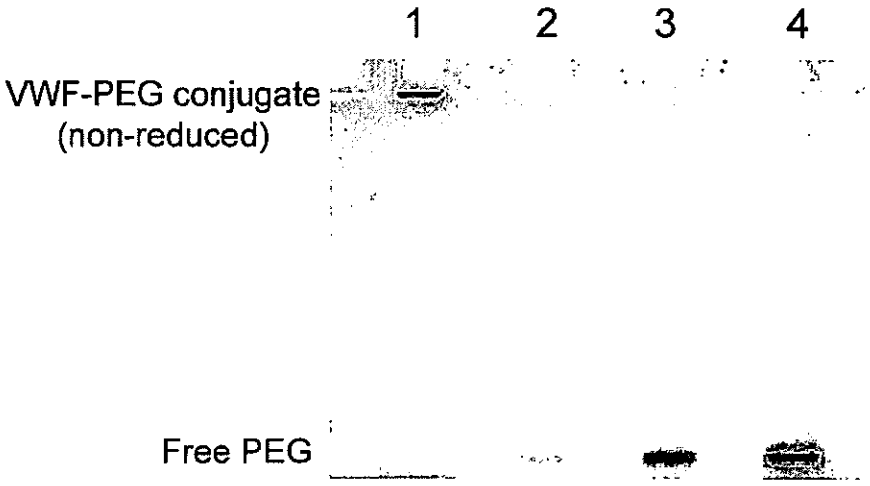


Figure 3C

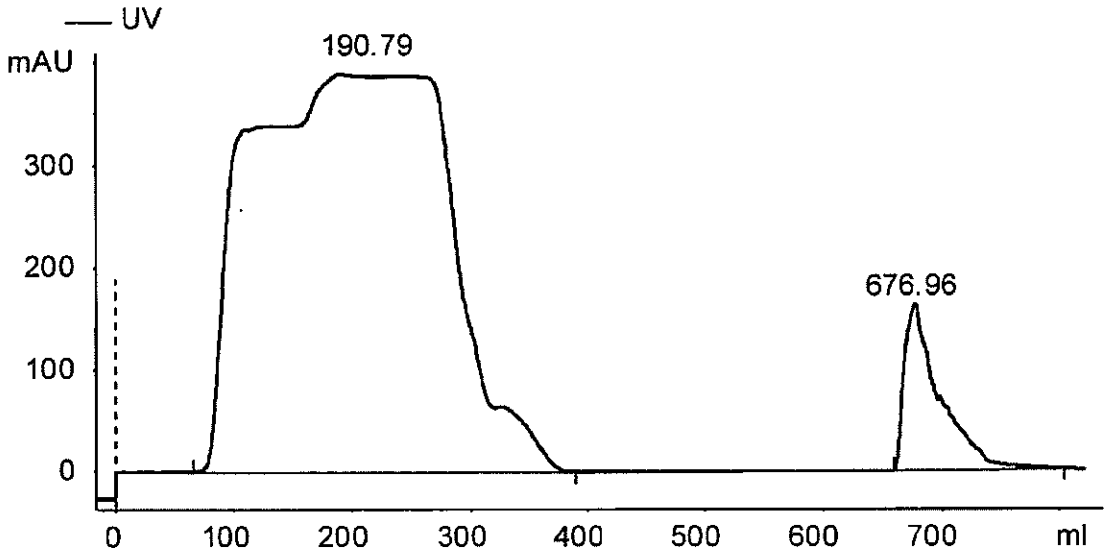


Figure 4A

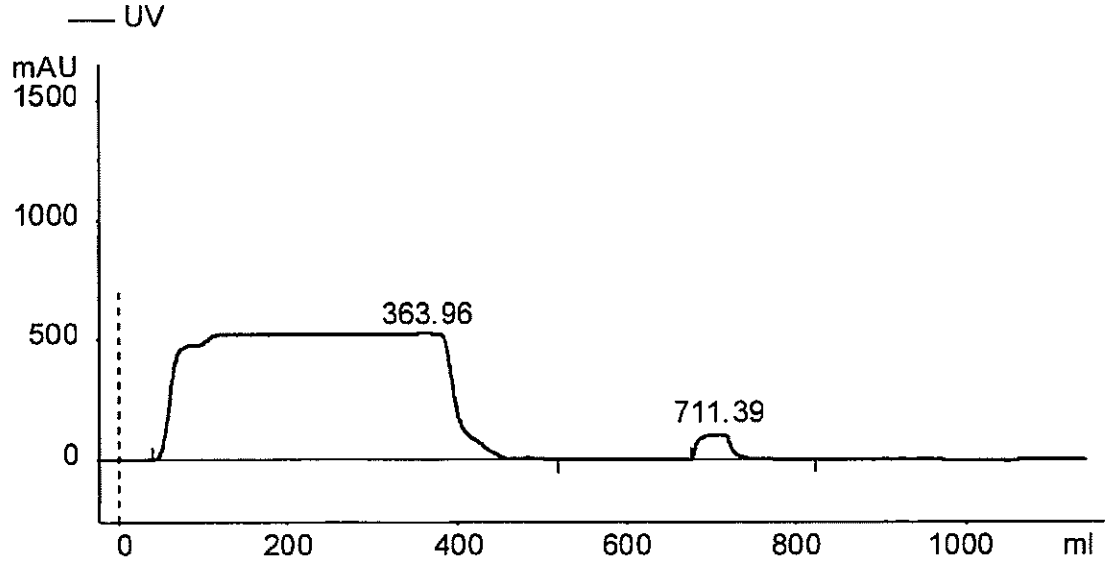


Figure 4B

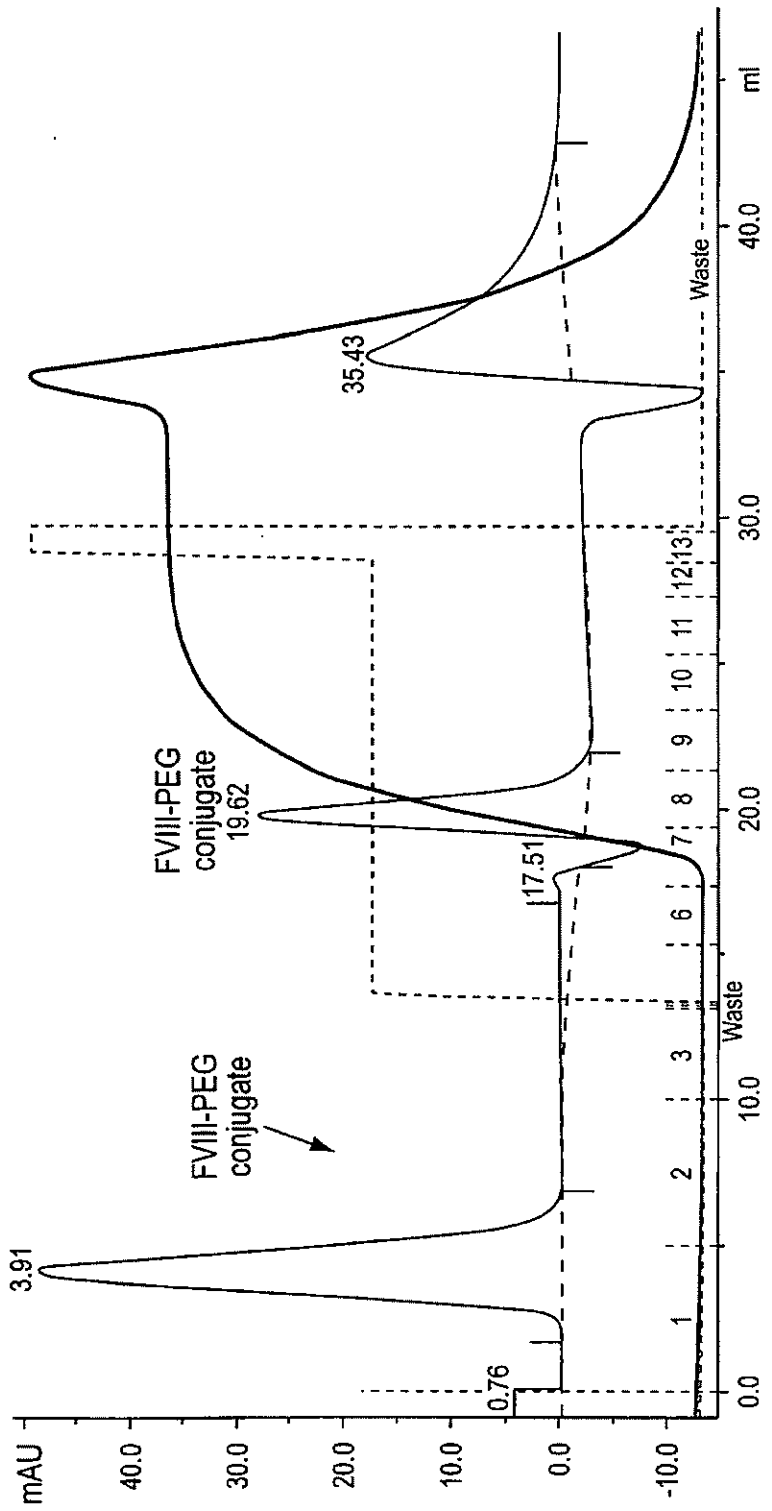

mAU
40.0
30.0
20.0
10.0
0.0
-10.0
0.0
10.0
20.0
30.0
40.0
ml
Waste
Waste
3.91
0.76
17.51
FVIII-PEG conjugate
19.62
FVIII-PEG conjugate
35.43
1
2
3
6
7
8
9
10
11
12
13

Figure 5

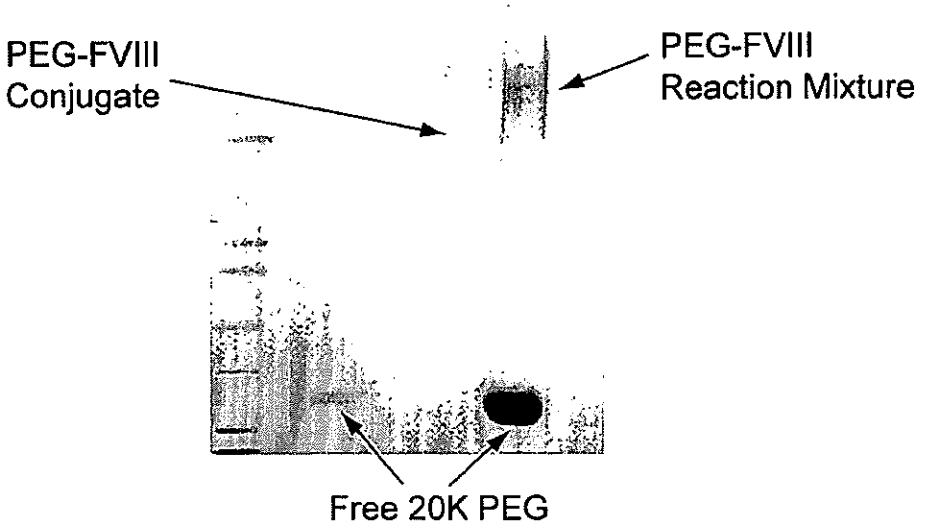


Figure 6A

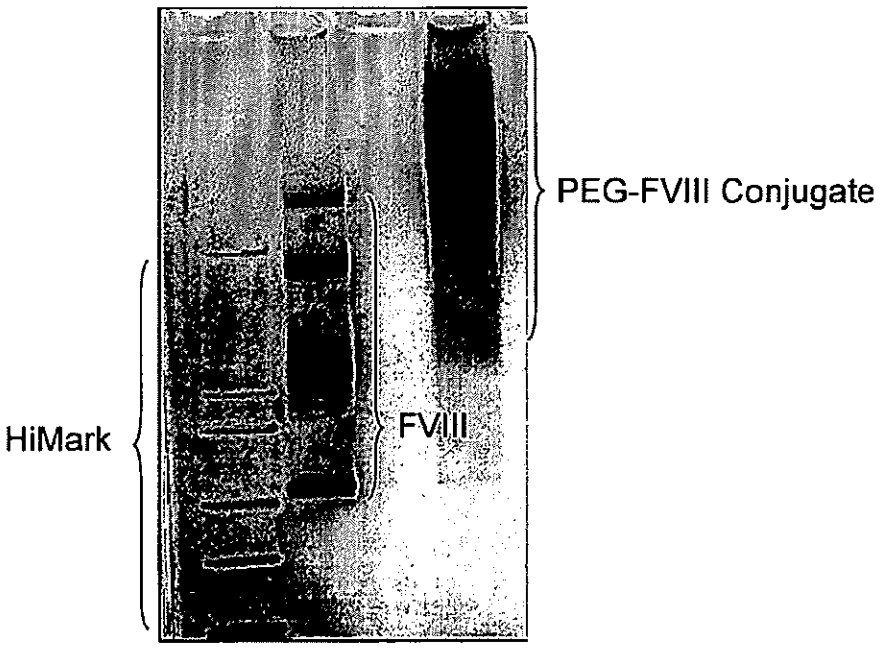


Figure 6B

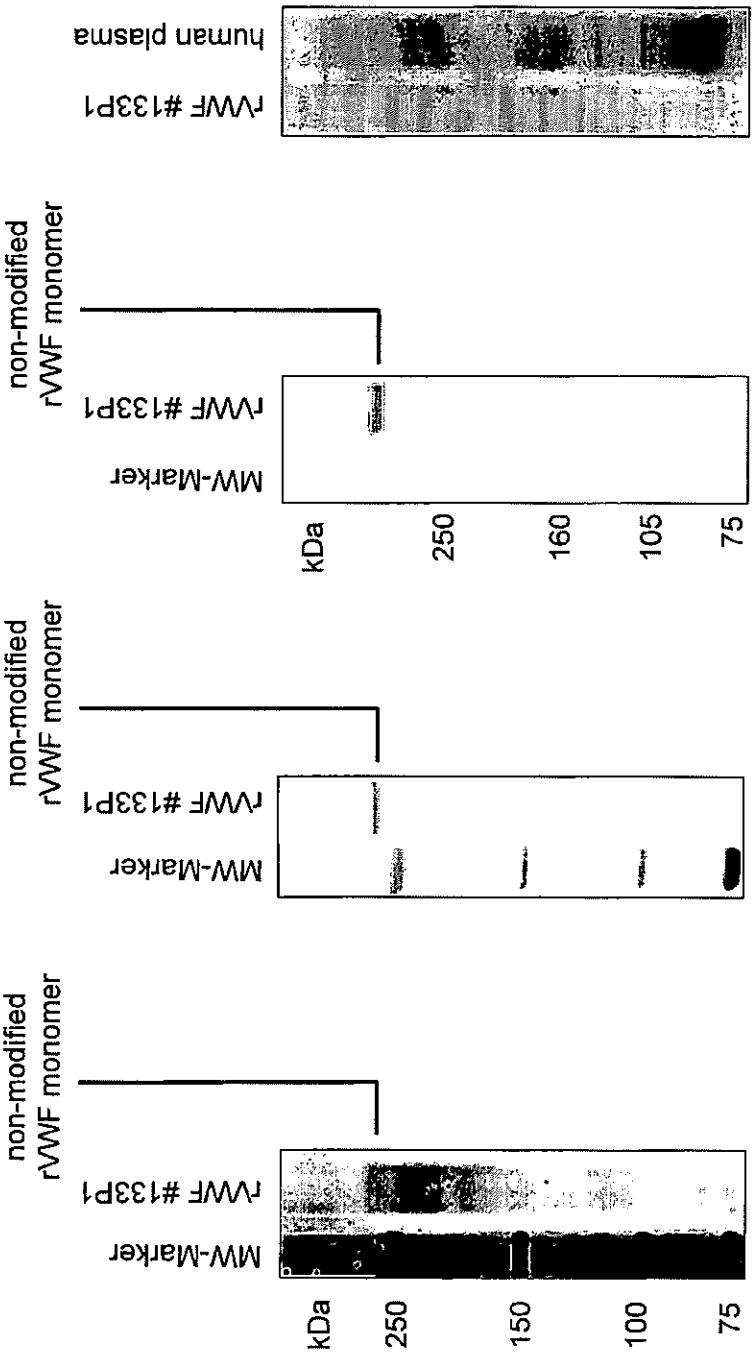


Figure 7A

Figure 7B

Figure 7C

Figure 7D

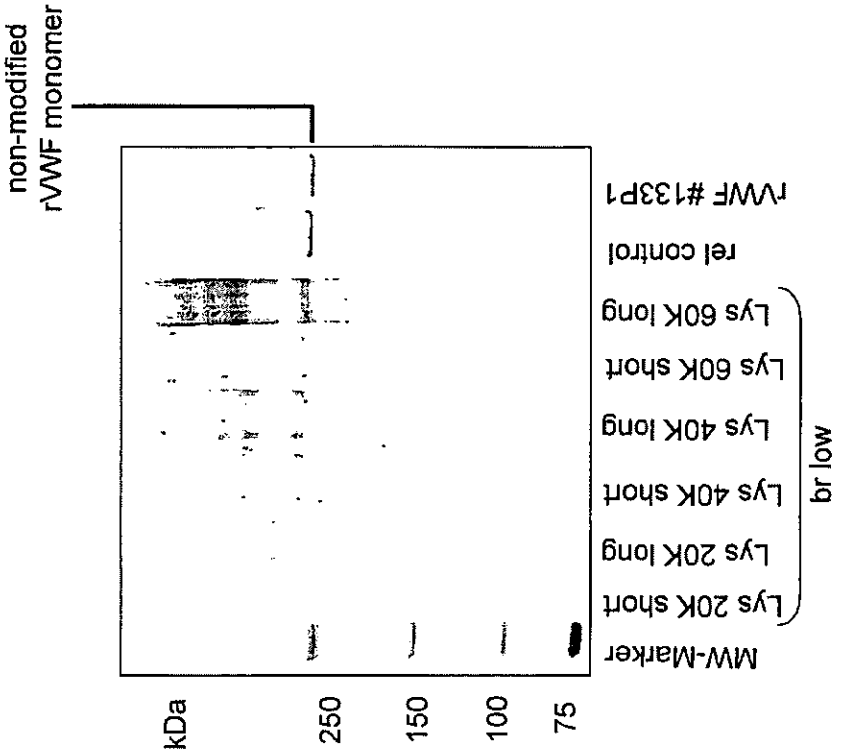


Figure 8B

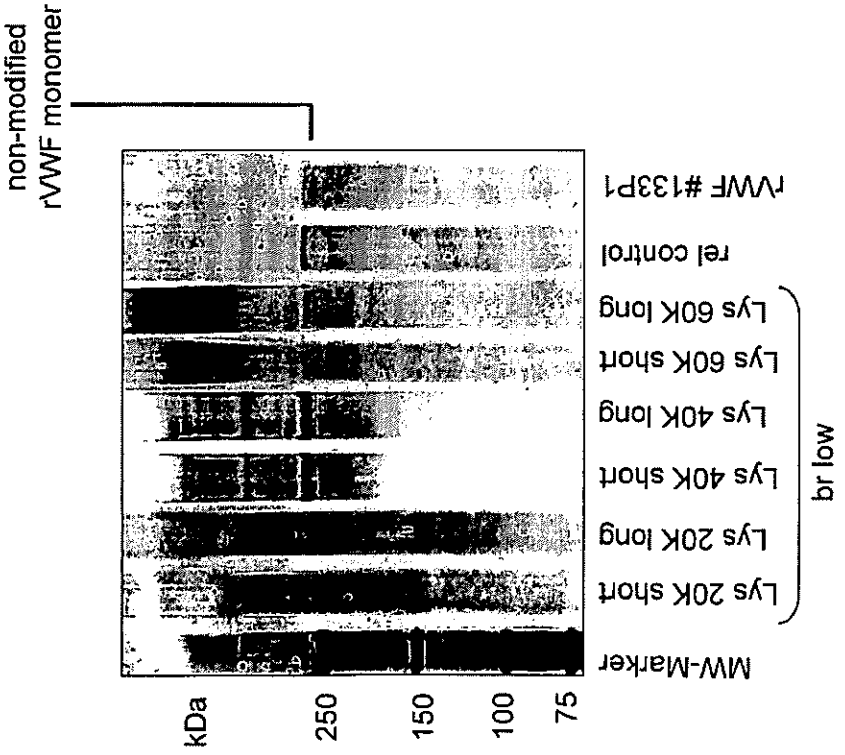


Figure 8A

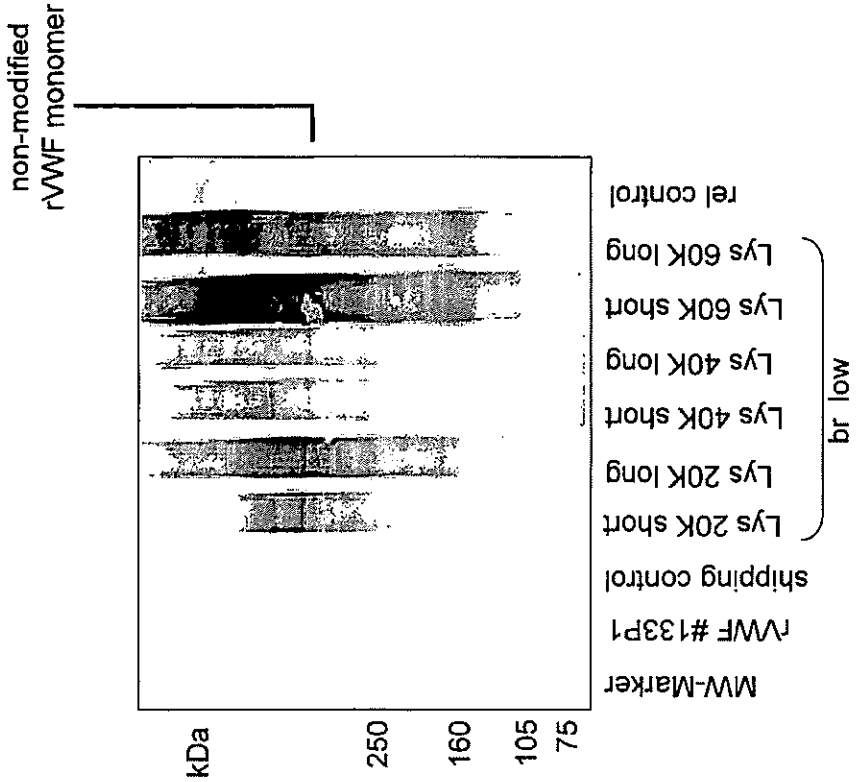


Figure 9B

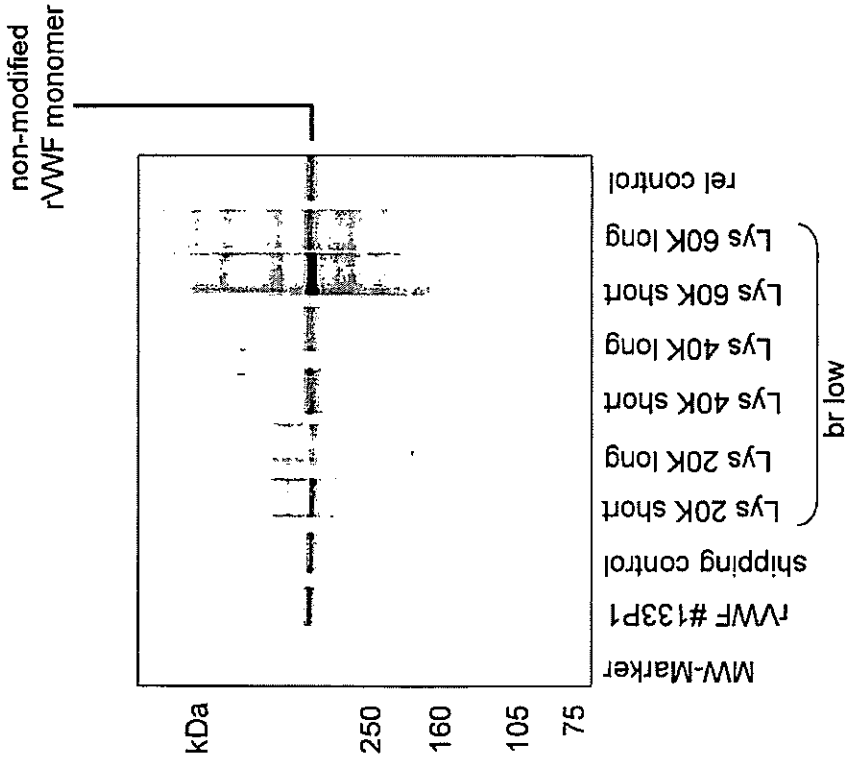


Figure 9A

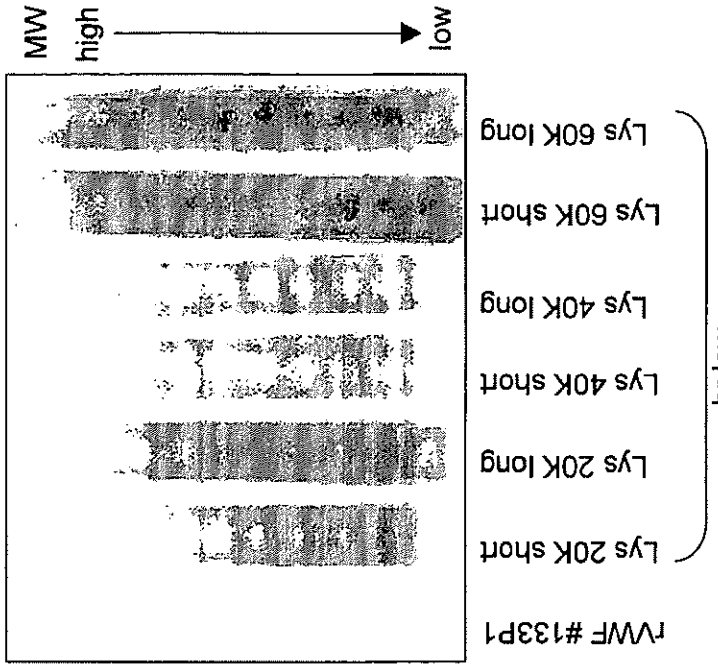


Figure 10B

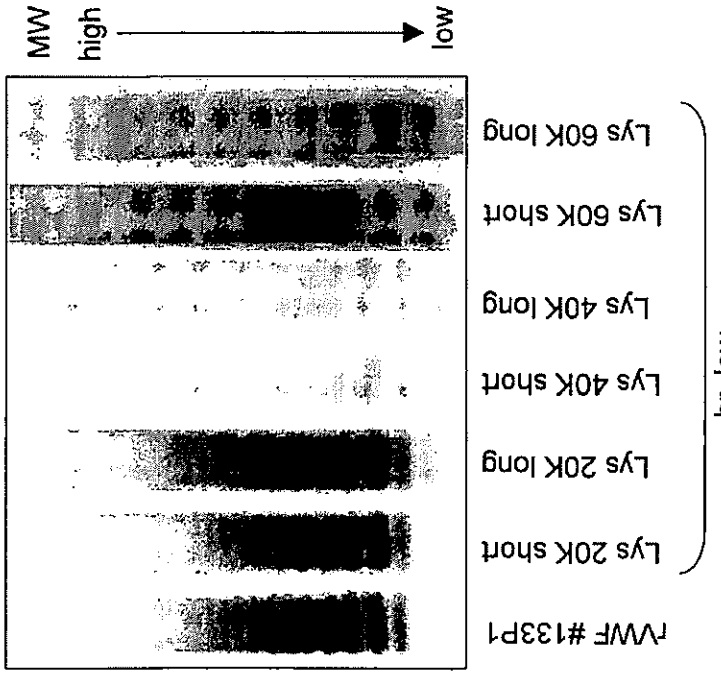


Figure 10A

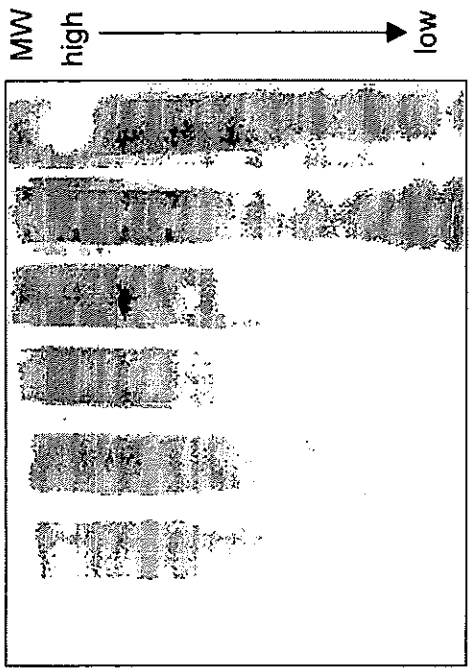


Figure 11B

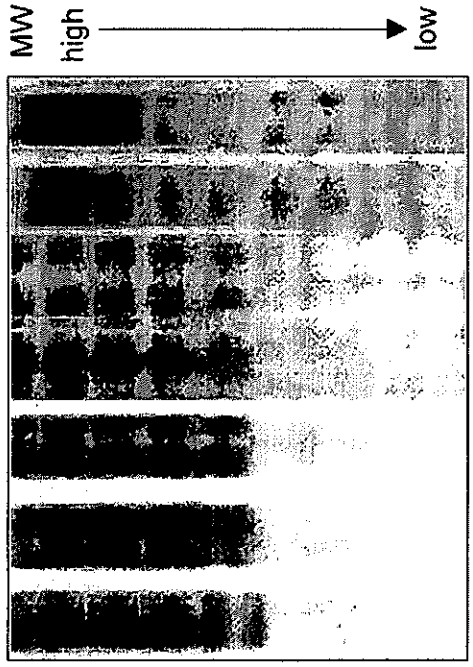


Figure 11A

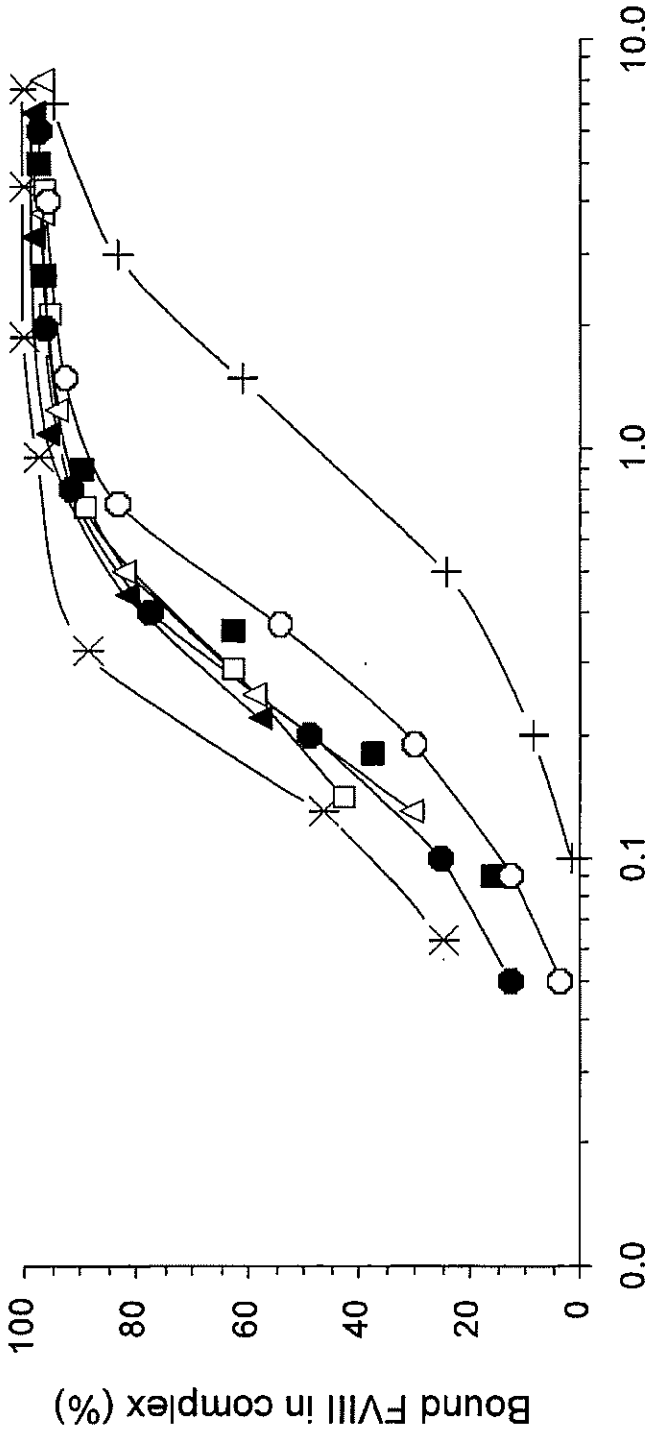

Bound FVIII in complex (%)
100
80
60
40
20
0
0.0
0.1
1.0
10.0
µg VWF / U FVIII

Figure 12

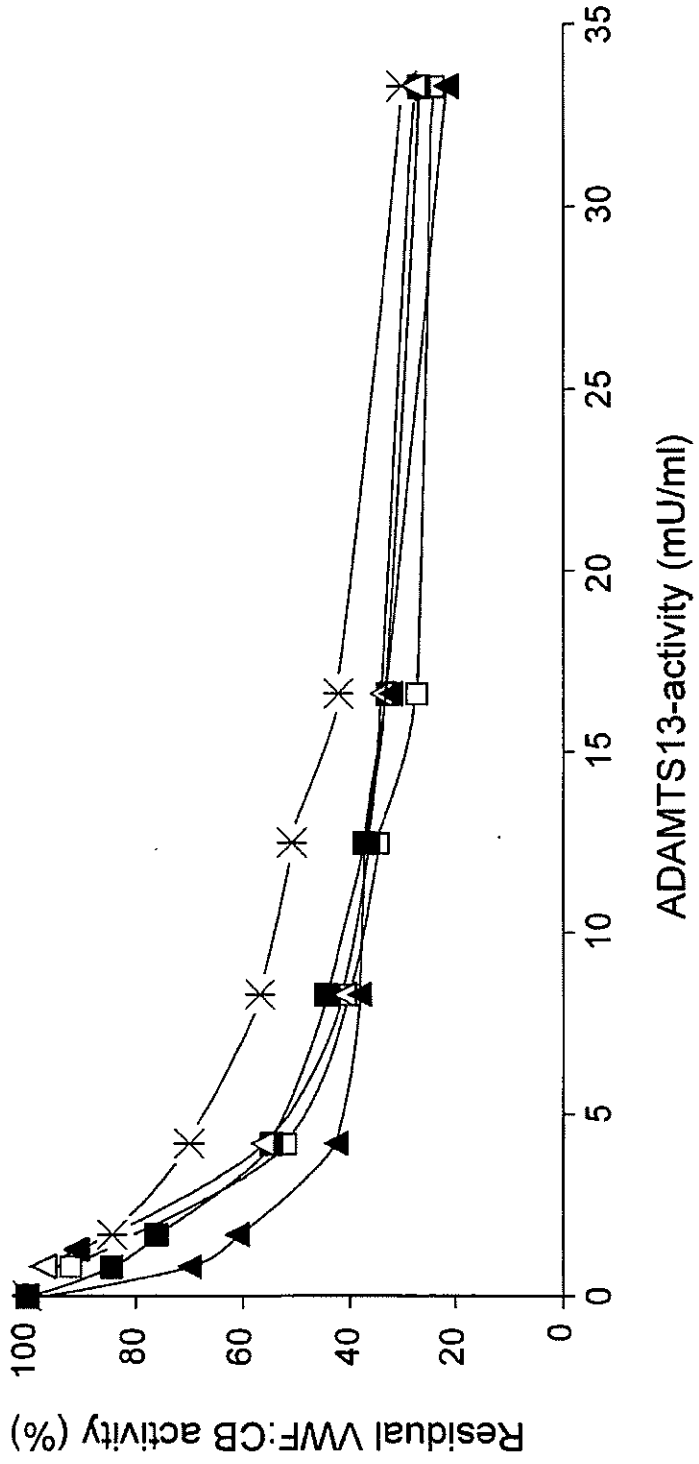

Residual VWF:CB activity (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
35
ADAMTS13-activity (mU/ml)

Figure 13

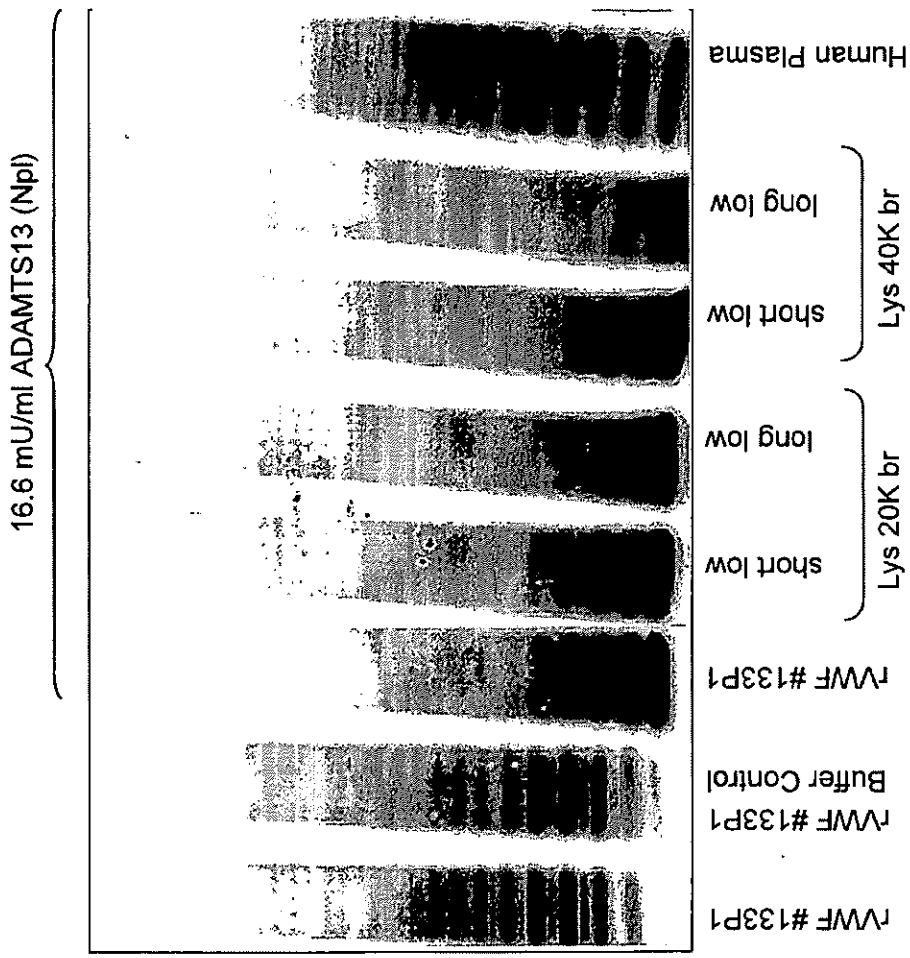

16.6 mU/ml ADAMTS13 (Npl)
rVWF #133P1
rVWF #133P1
Buffer Control
rVWF #133P1
short low
long low
Lys 20K br
short low
long low
Lys 40K br
Human Plasma

Figure 14

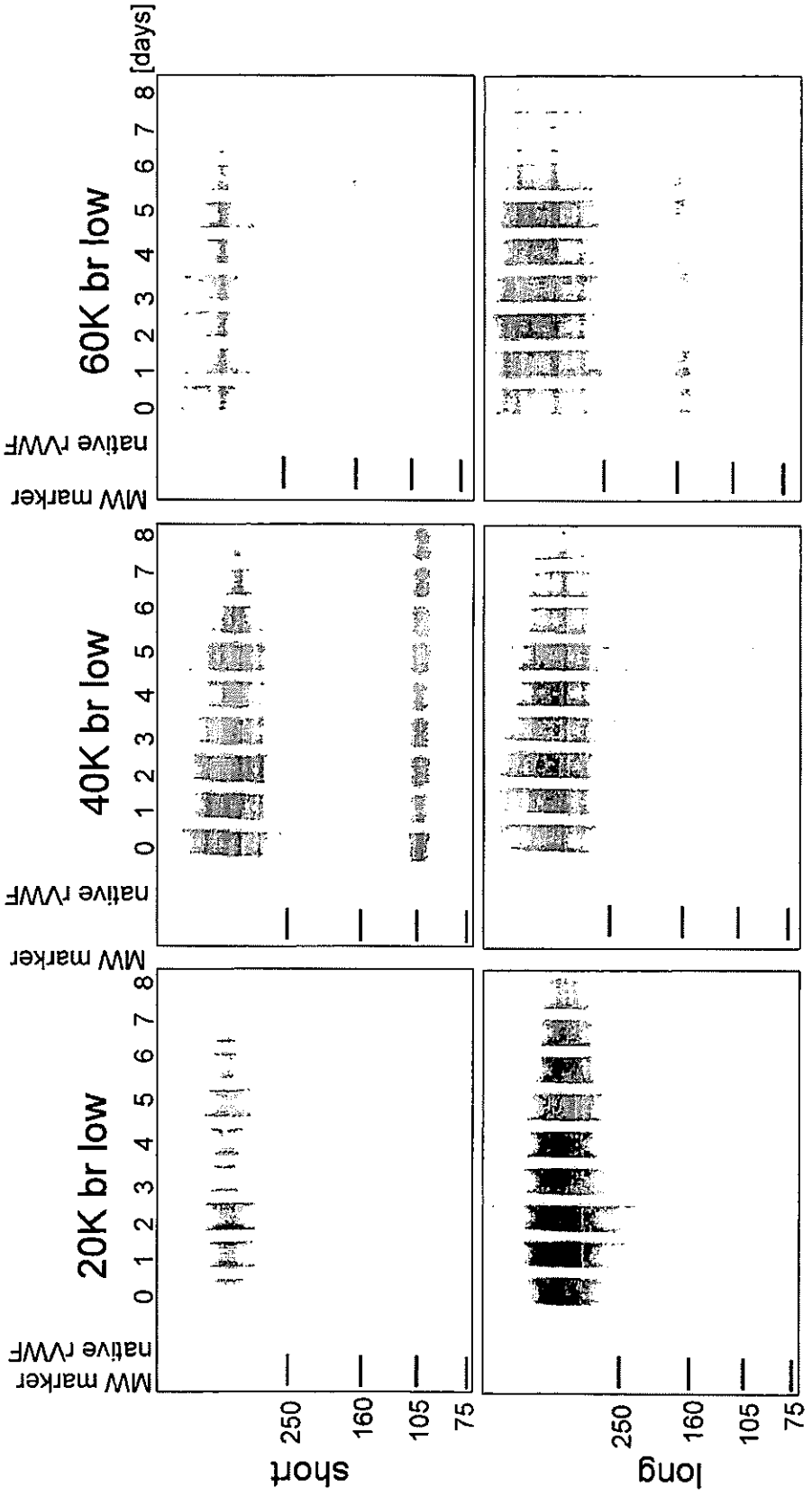

20K br low
40K br low
60K br low
MW marker
native rVWF
0 1 2 3 4 5 6 7 8 [days]
short
long
250
160
105
75

Figure 15

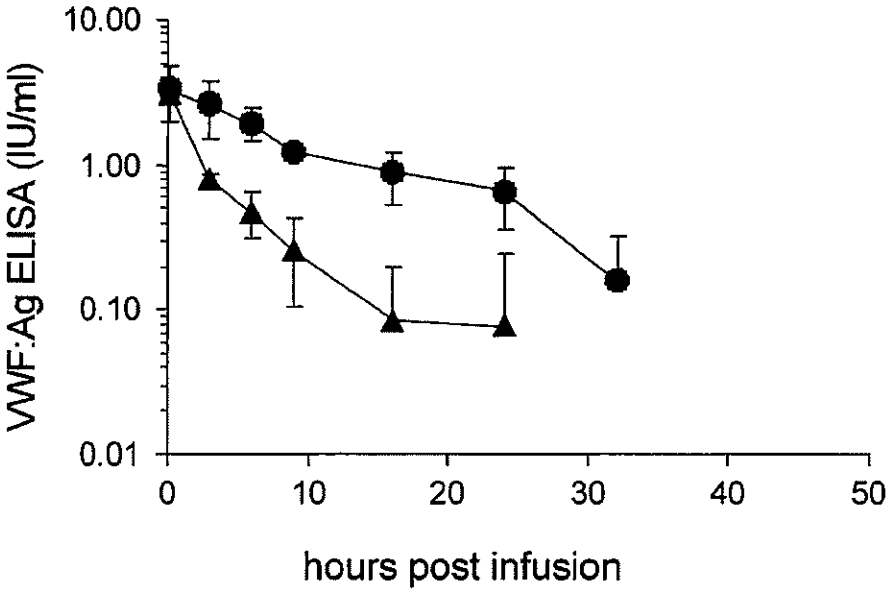


Figure 16A

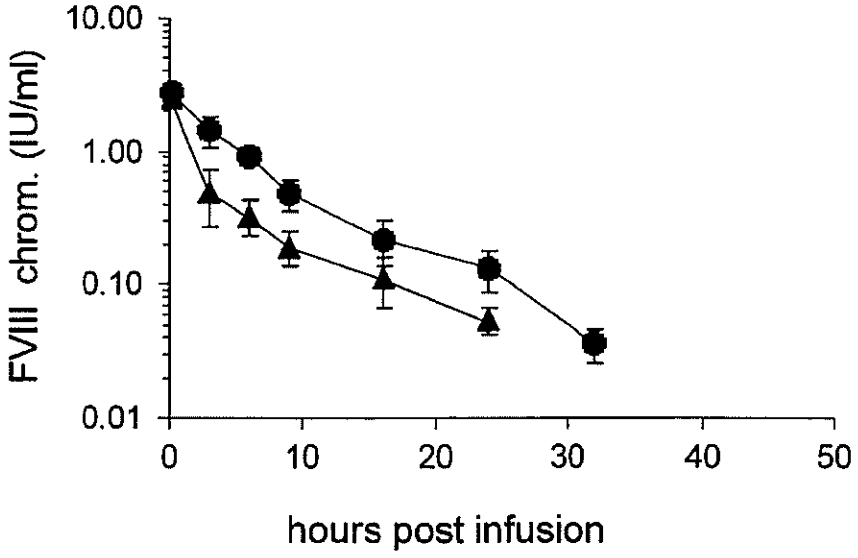


Figure 16B

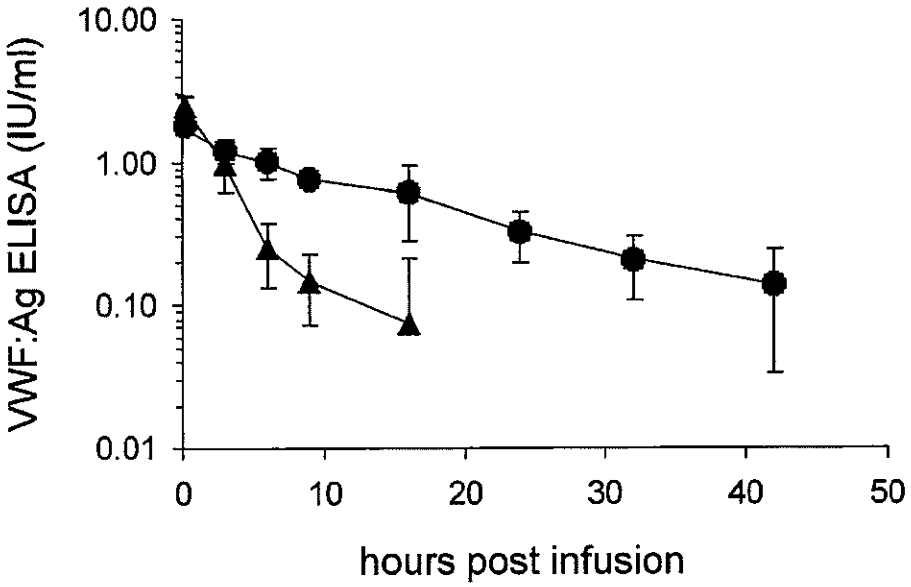


Figure 17A

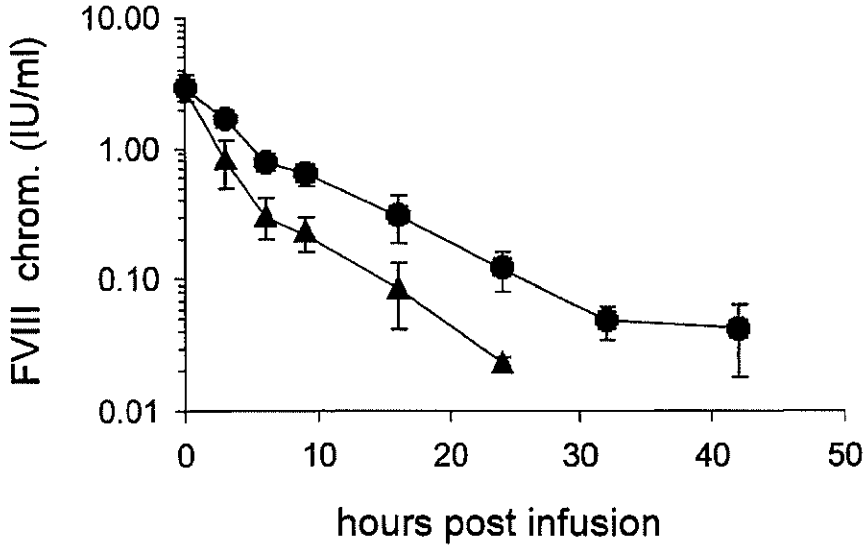


Figure 17B

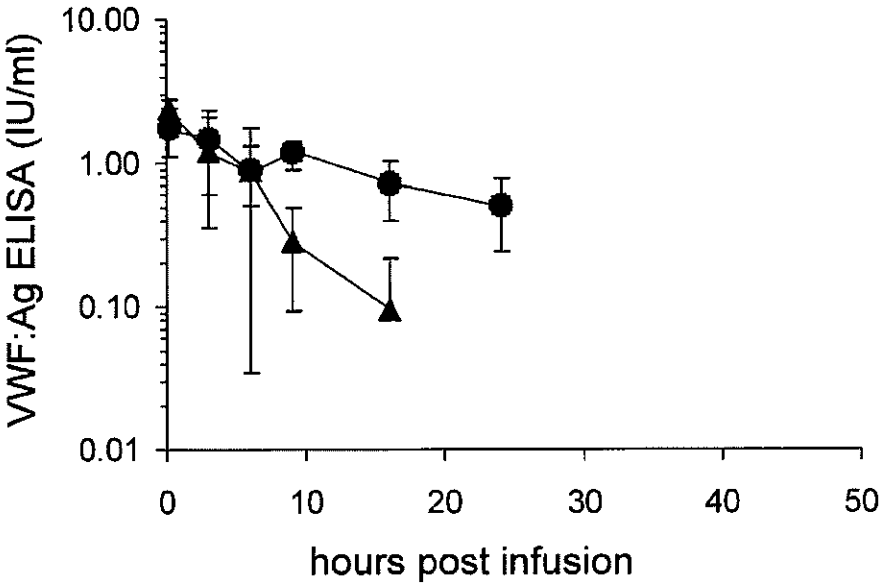


Figure 18A

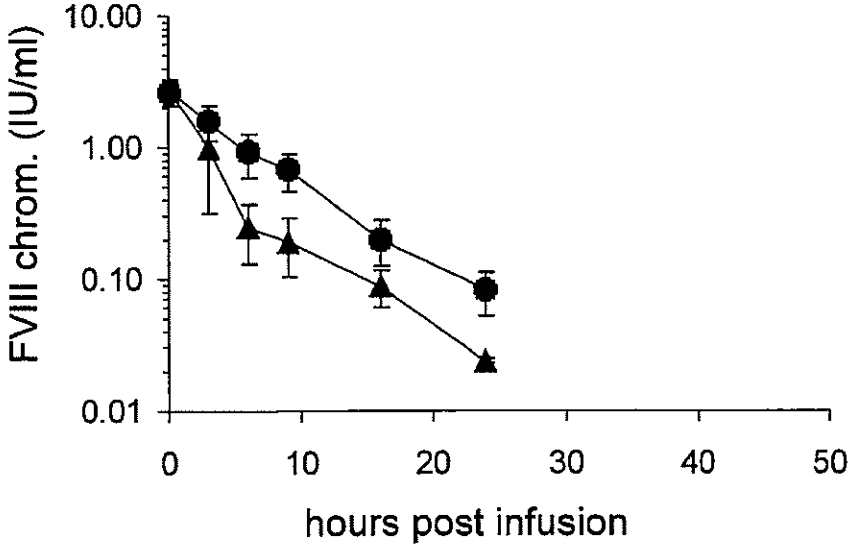


Figure 18B

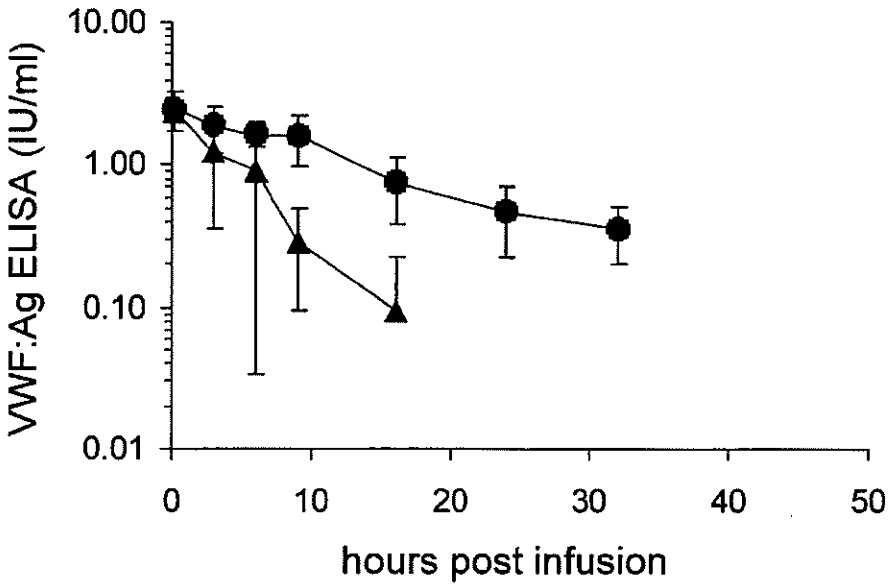


Figure 19A

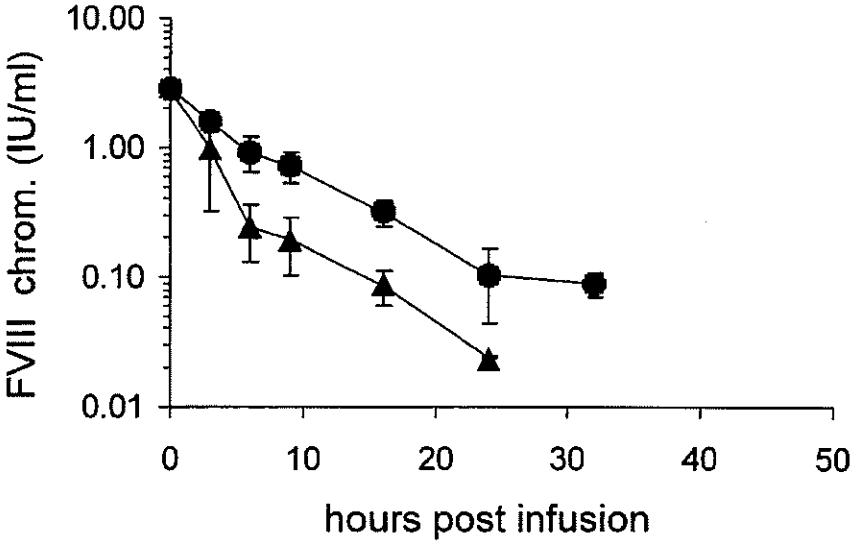


Figure 19B

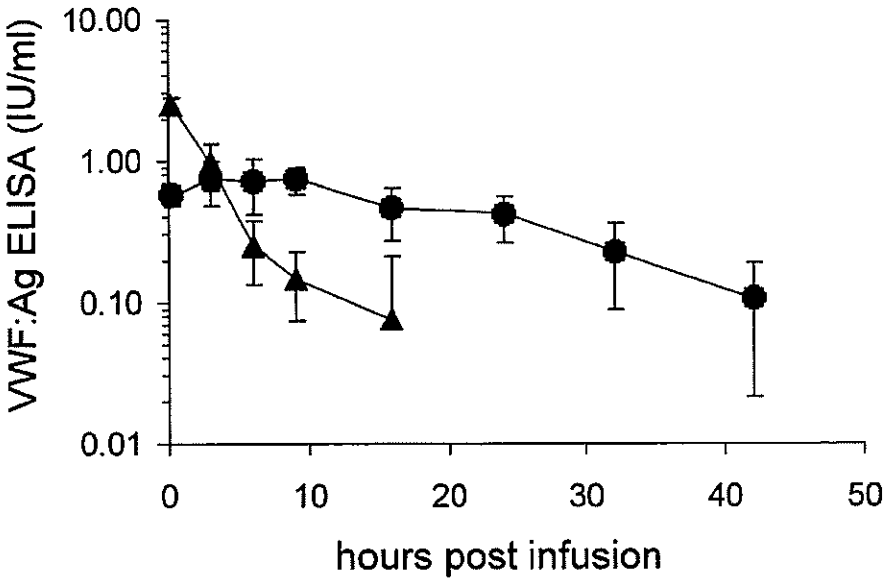


Figure 20A

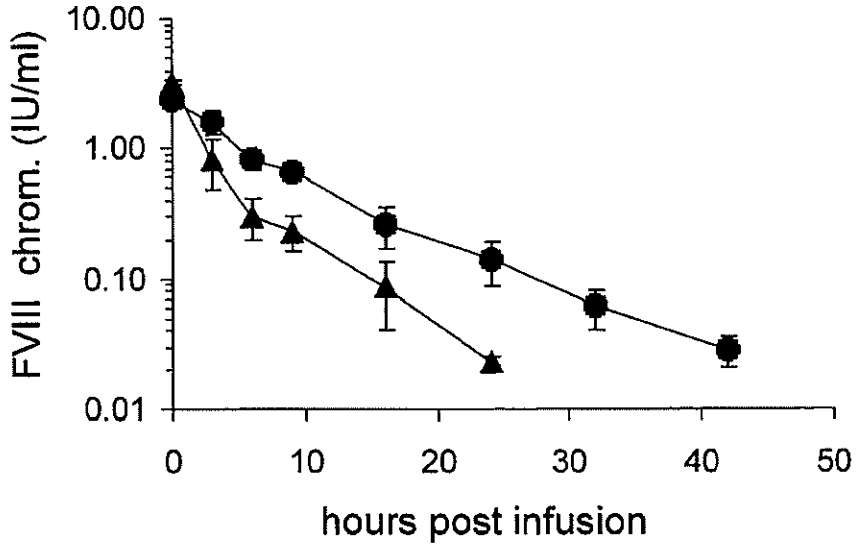


Figure 20B

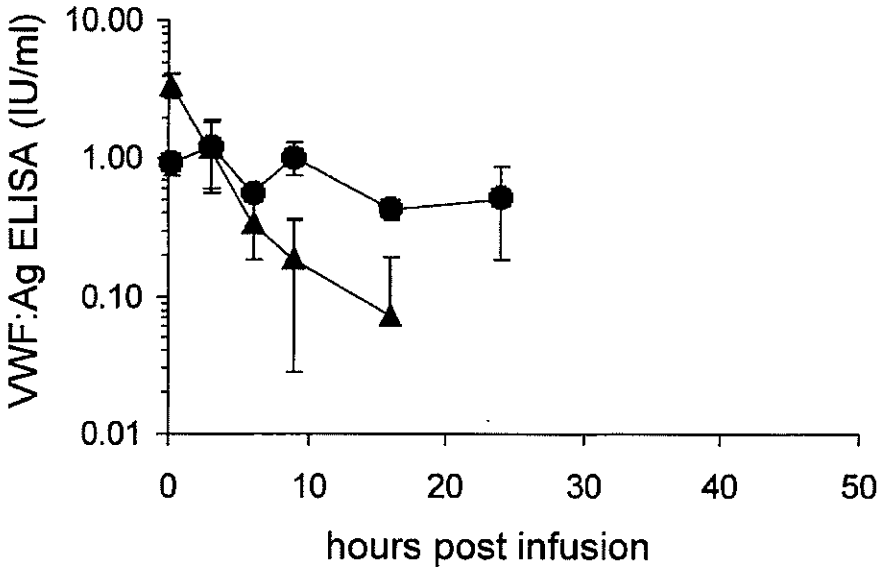


Figure 21A

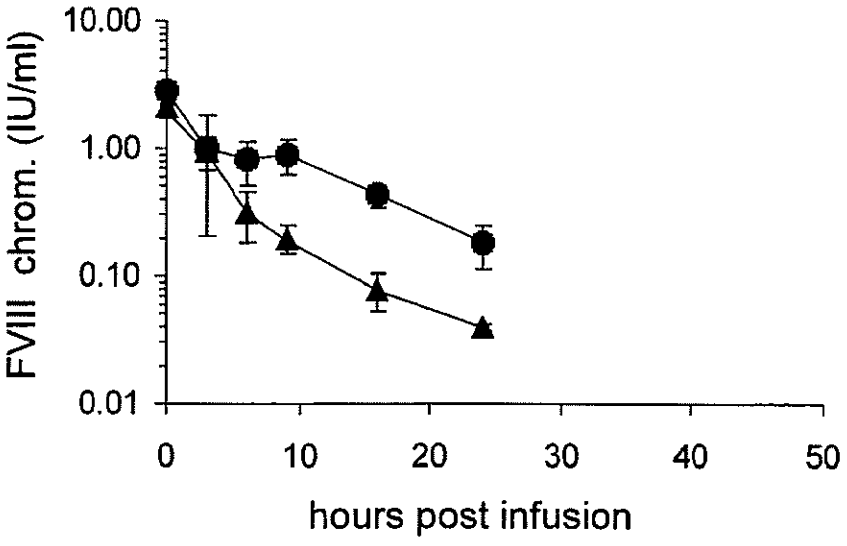


Figure 21B

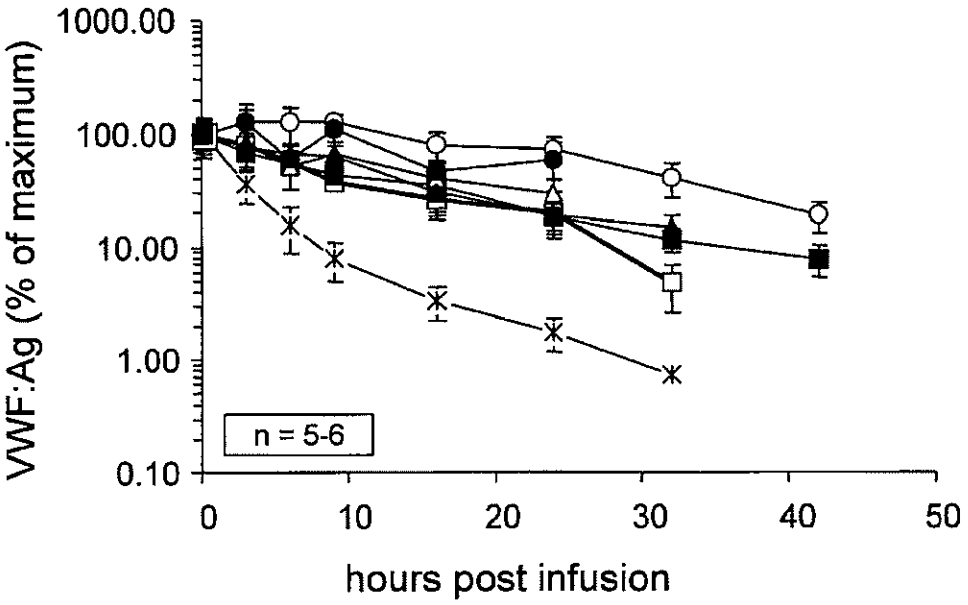


Figure 22A

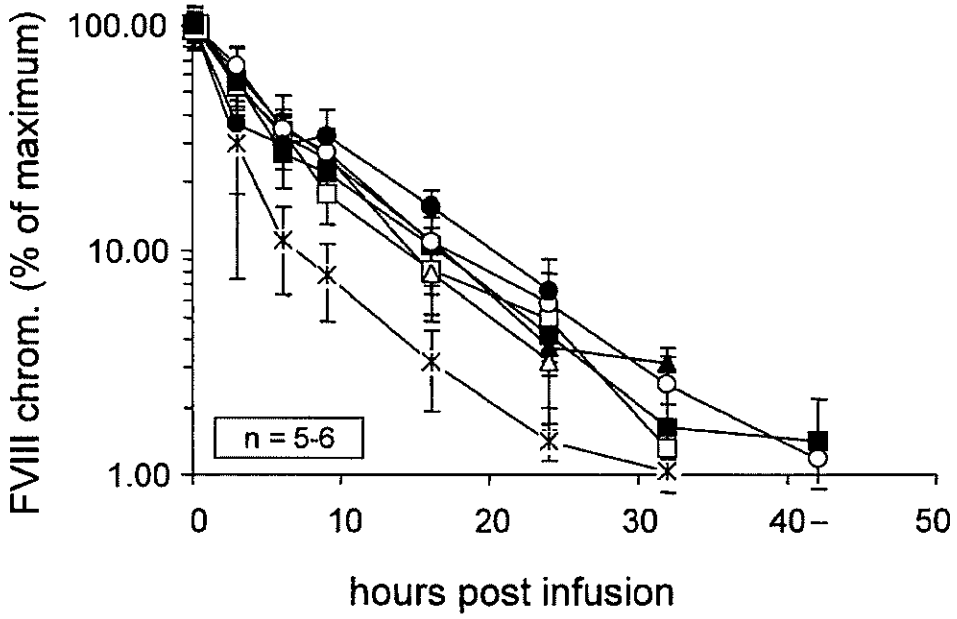


Figure 22B

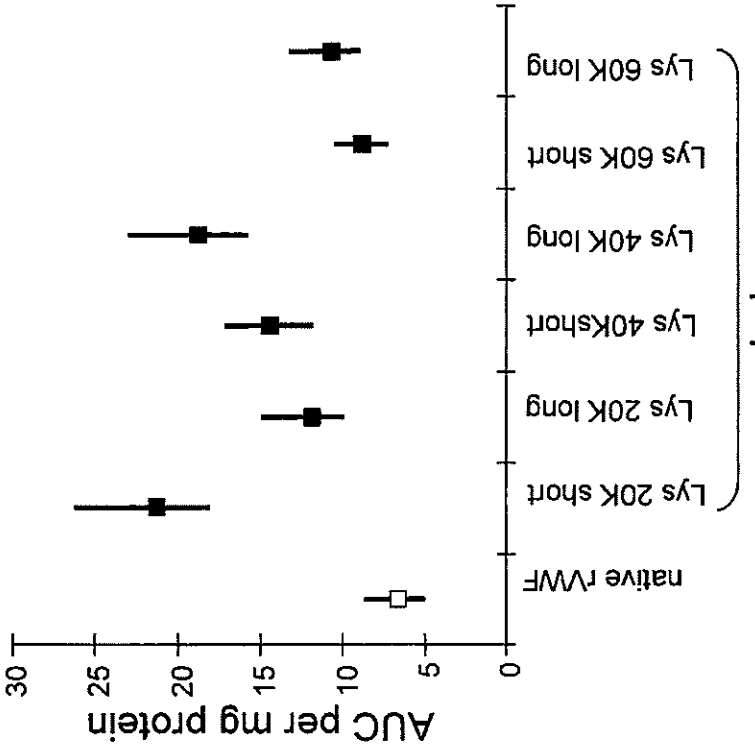


Figure 23B

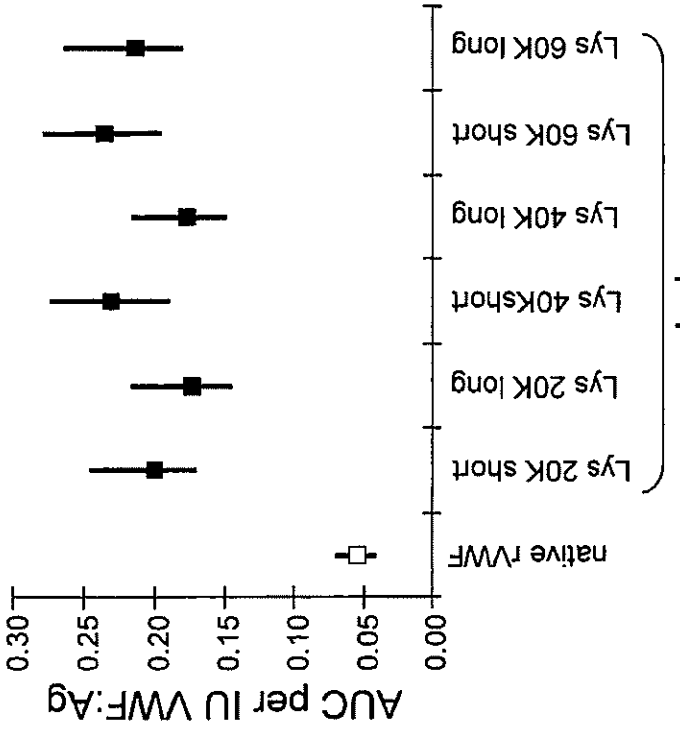


Figure 23A

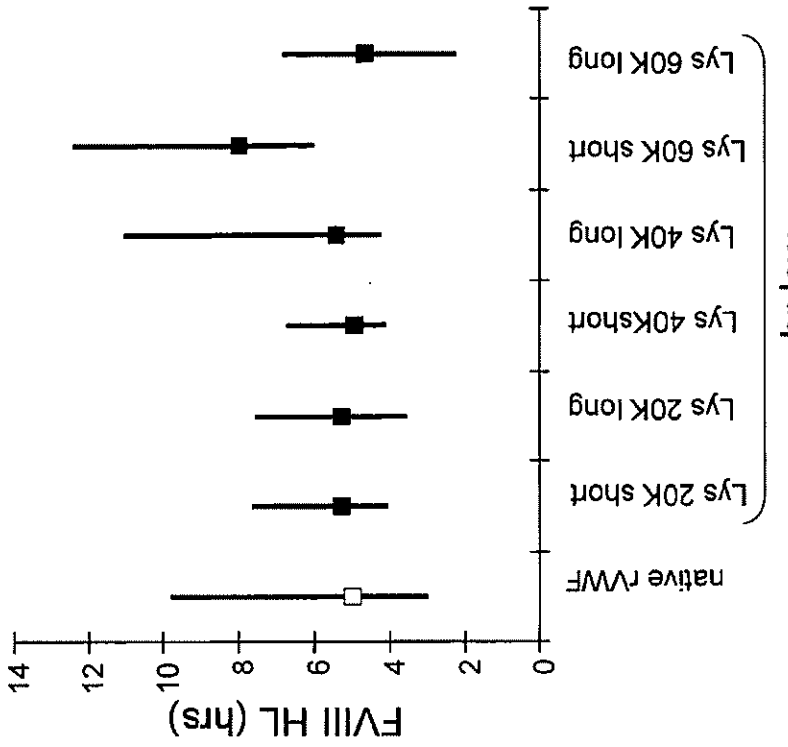


Figure 24B

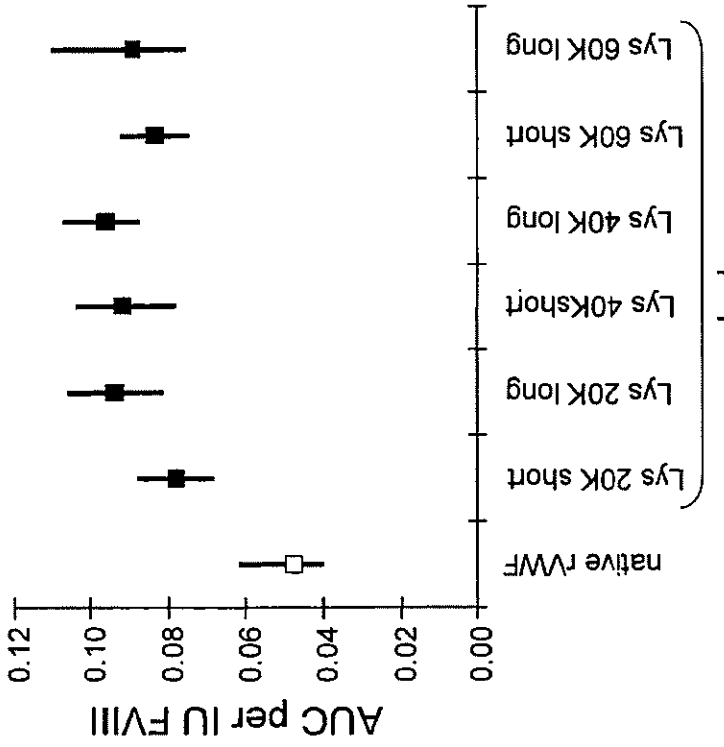


Figure 24A

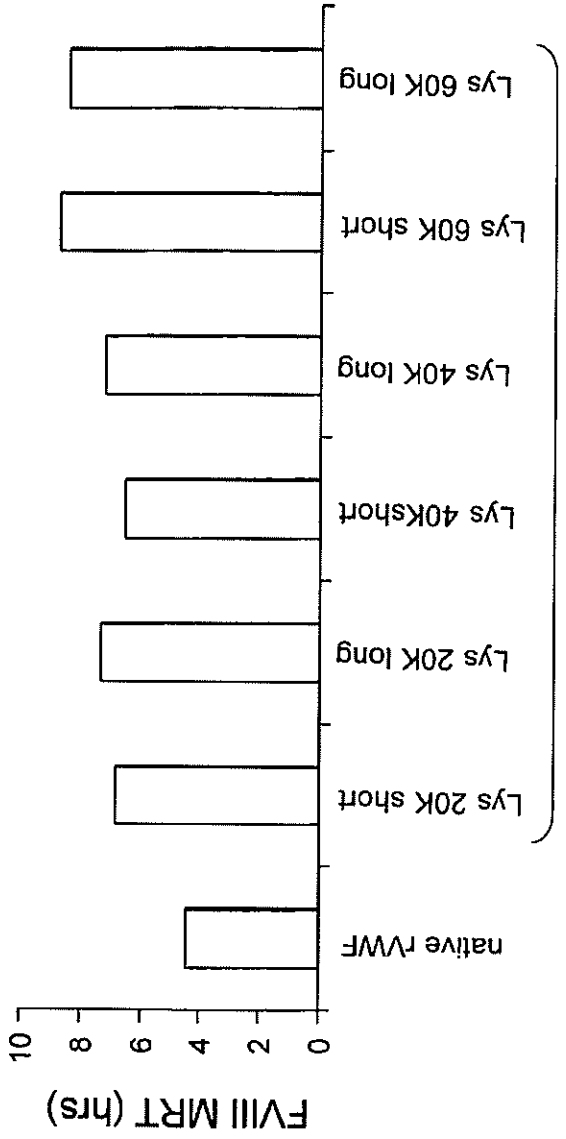

FVIII MRT (hrs)
0
2
4
6
8
10
native rVWF
Lys 20K short
Lys 20K long
Lys 40Kshort
Lys 40K long
Lys 60K short
Lys 60K long
br low

Figure 25

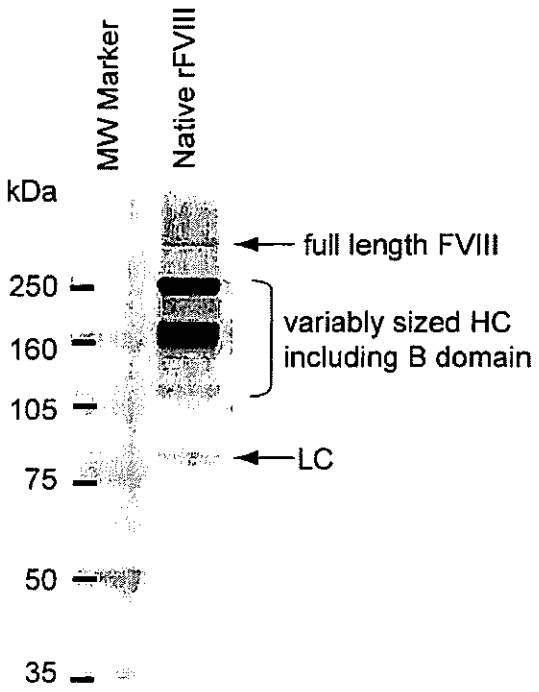

MW Marker
Native rFVIII
kDa
250
160
105
75
50
35
full length FVIII
variably sized HC
including B domain
LC

Figure 26

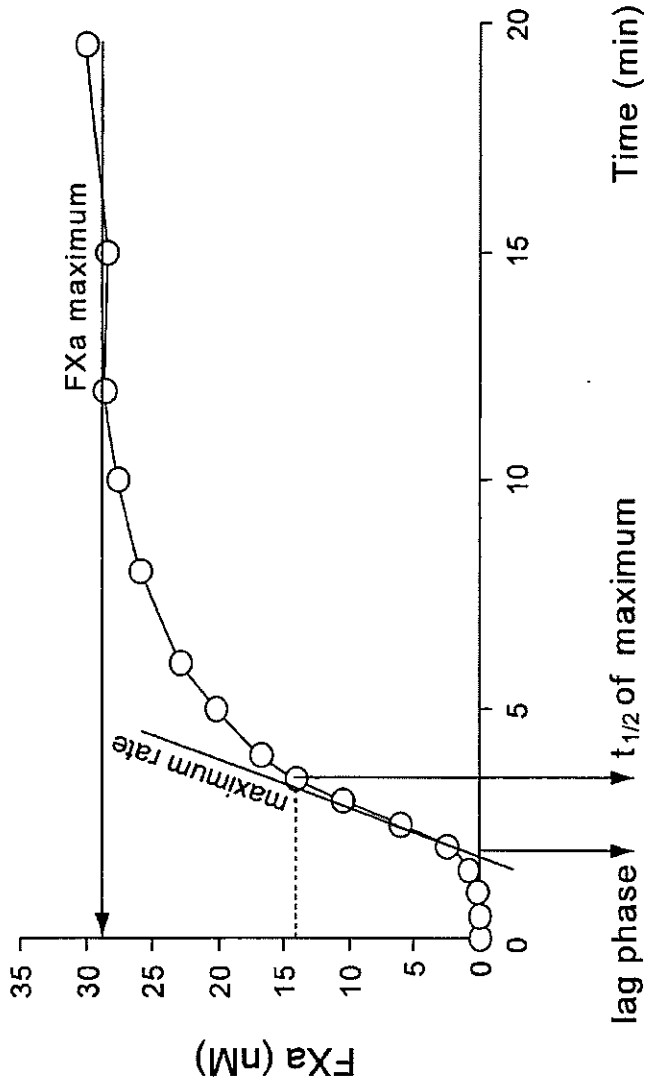

FXa maximum
maximum rate
lag phase
$t_{1/2}$ of maximum
Time (min)
FXa (nM)
0
5
10
15
20
25
30
35
0
5
10
15
20

Figure 27

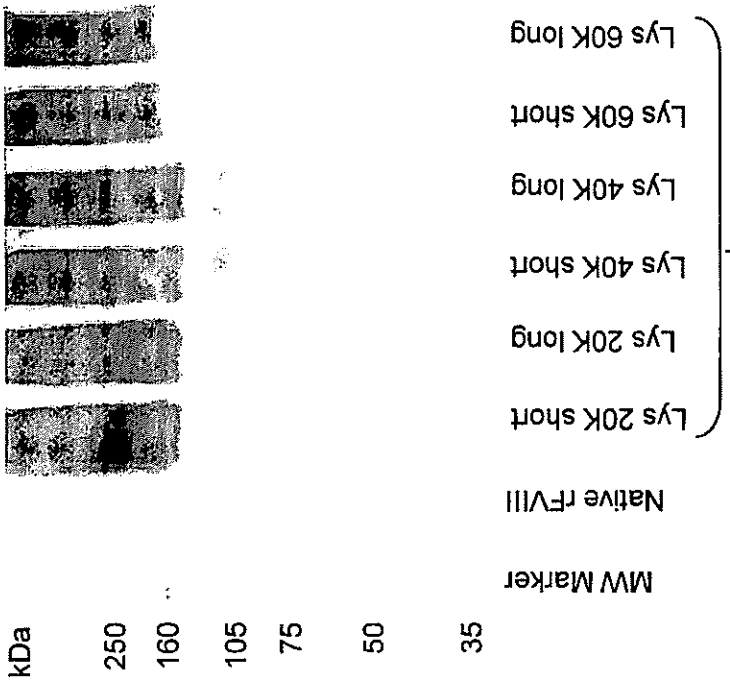


Figure 28B

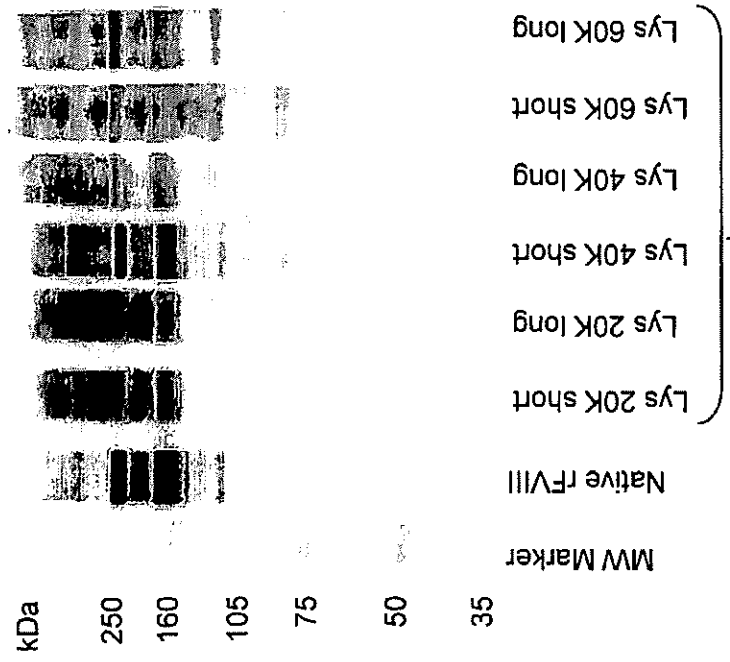


Figure 28A

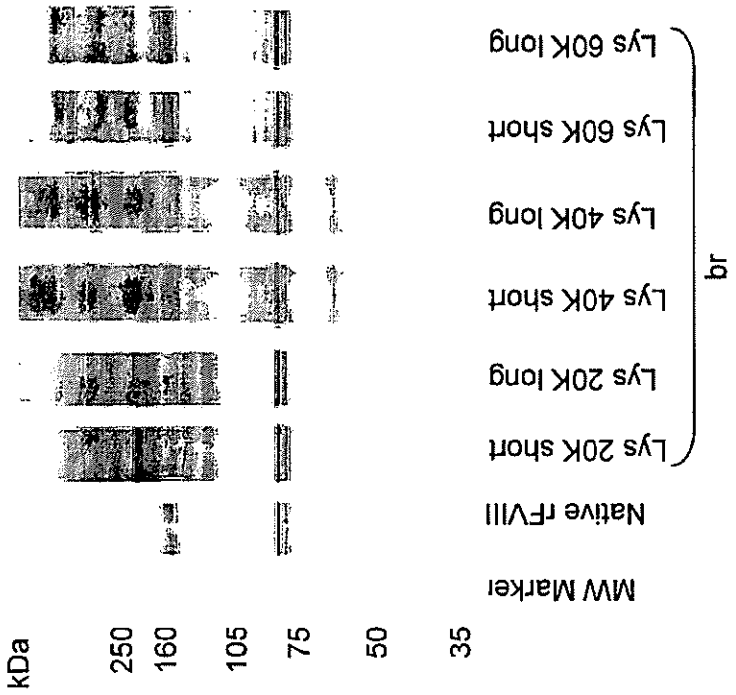


Figure 29B

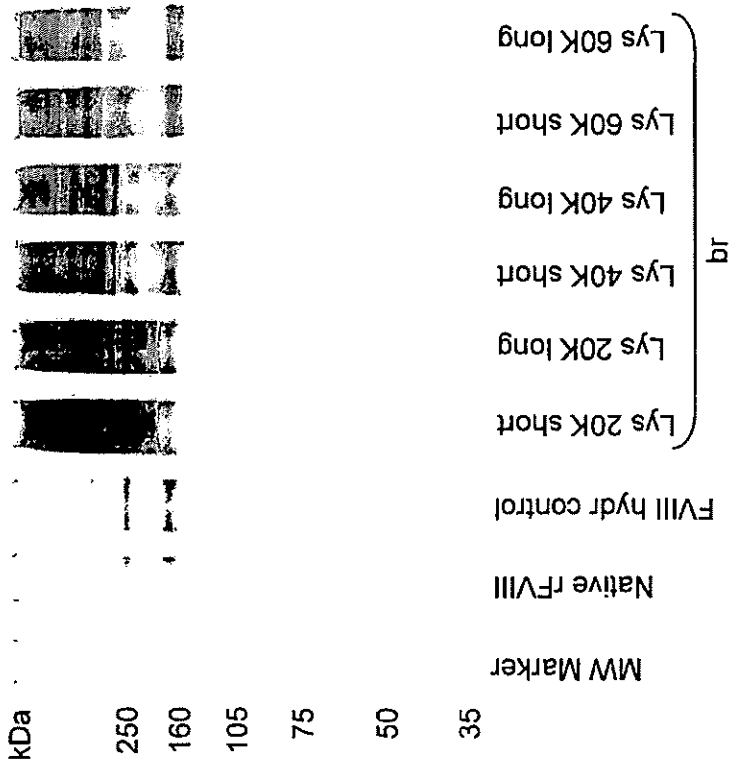


Figure 29A

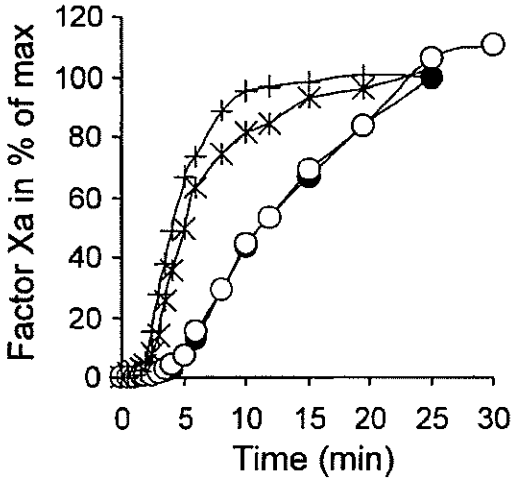


Figure 30A

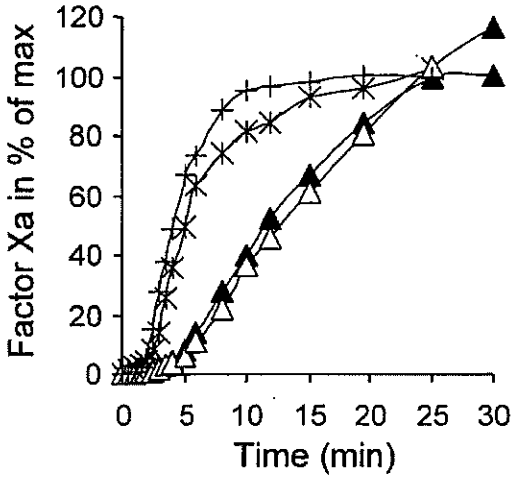


Figure 30B

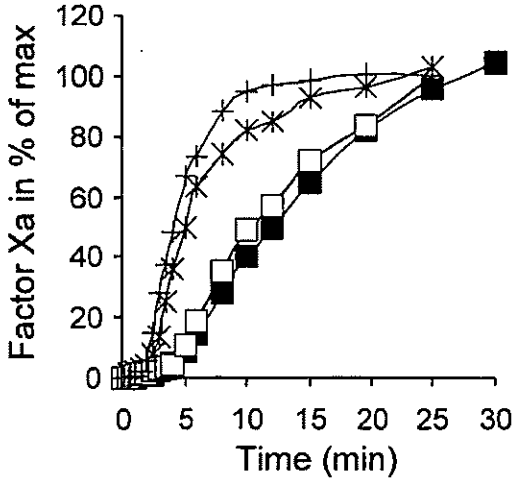


Figure 30C

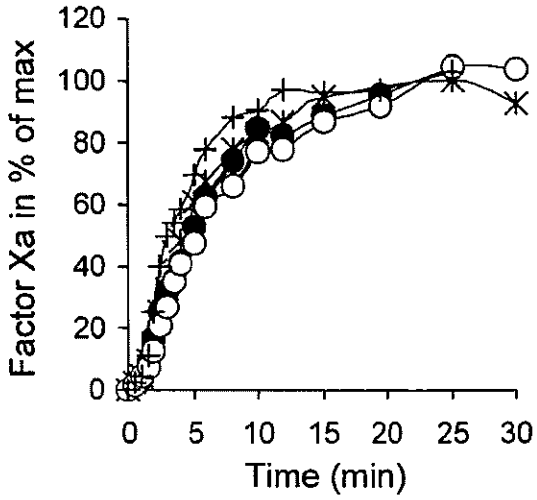


Figure 31A

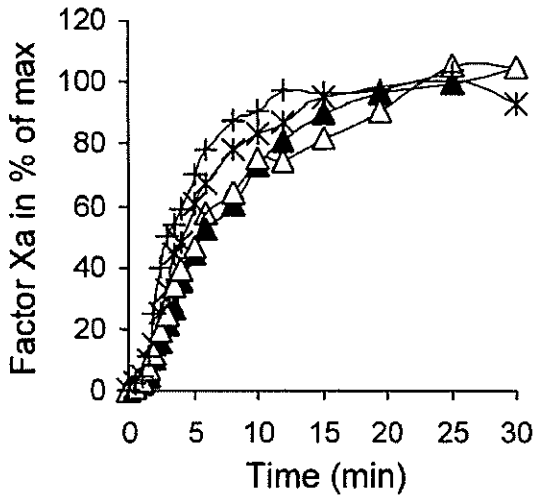


Figure 31B

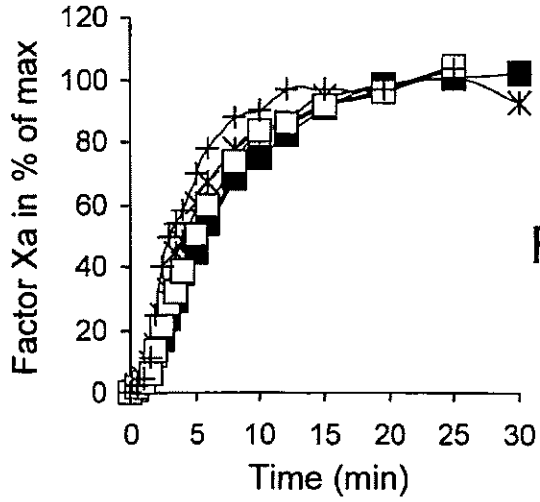


Figure 31C

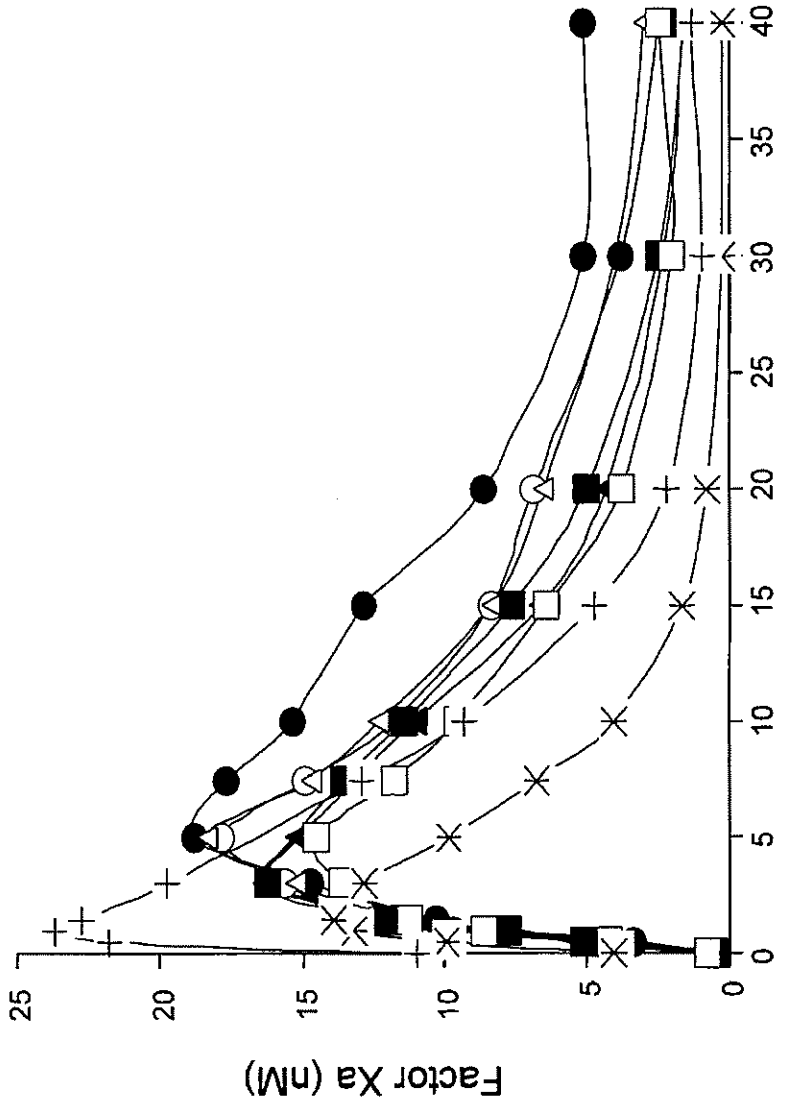


Figure 32

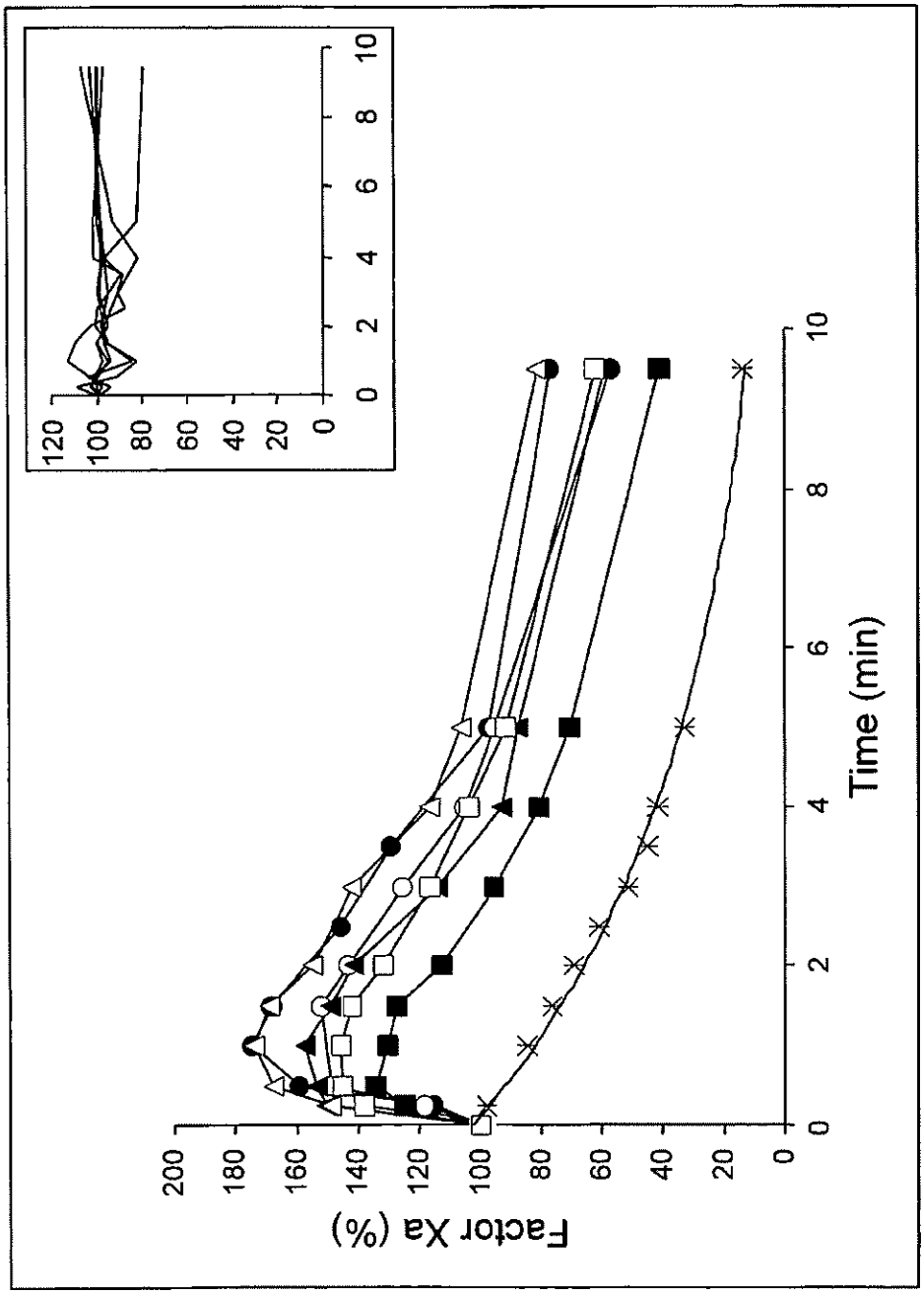


Figure 33

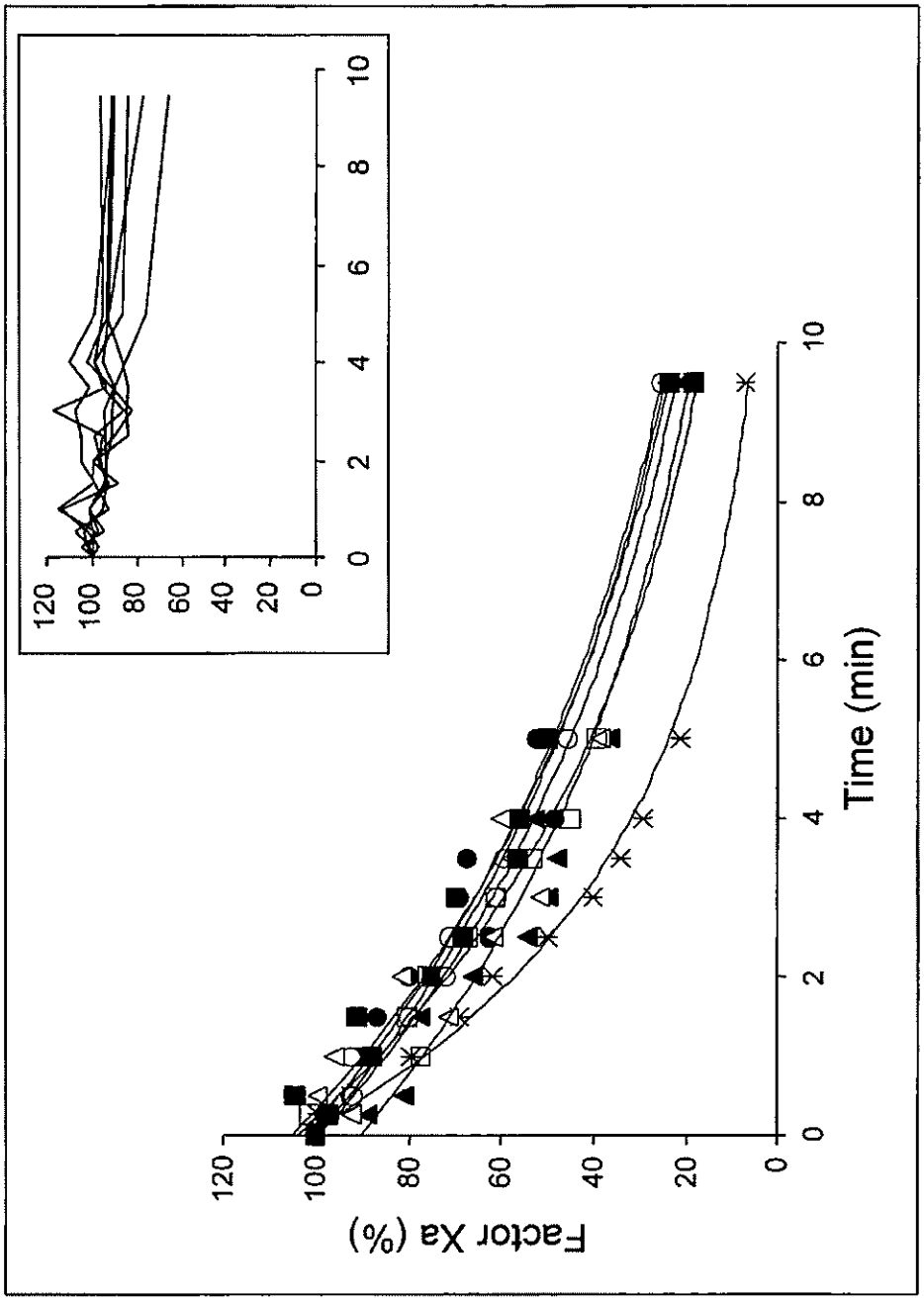


Figure 34

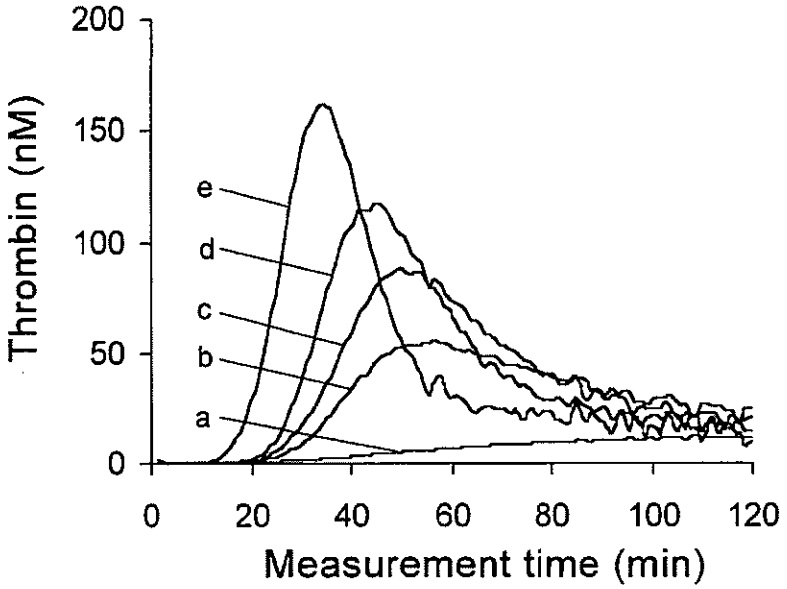


Figure 35A

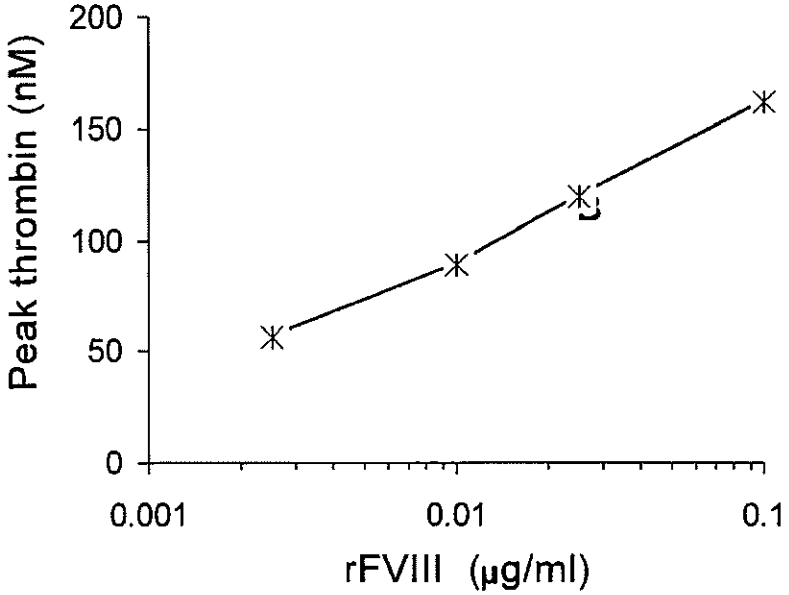


Figure 35B

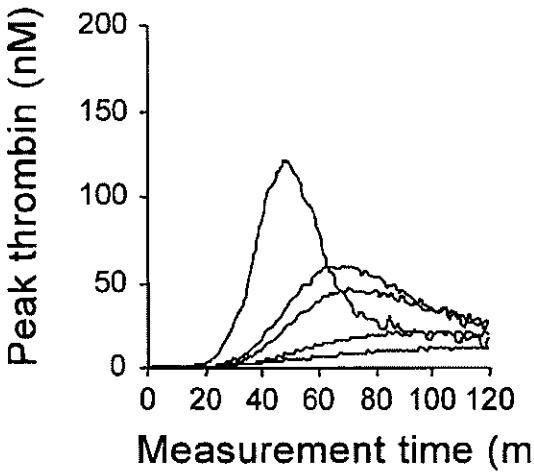


Figure 36A

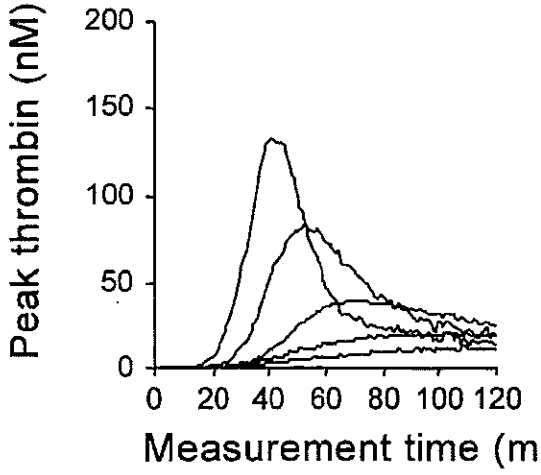


Figure 36B

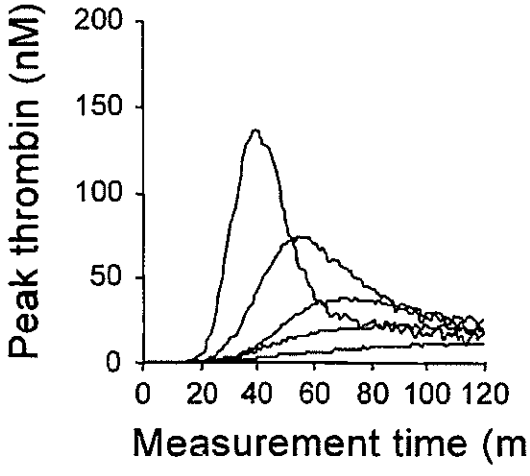


Figure 36C

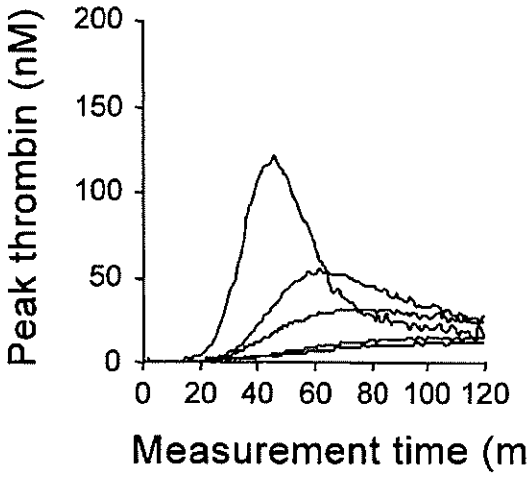


Figure 36D

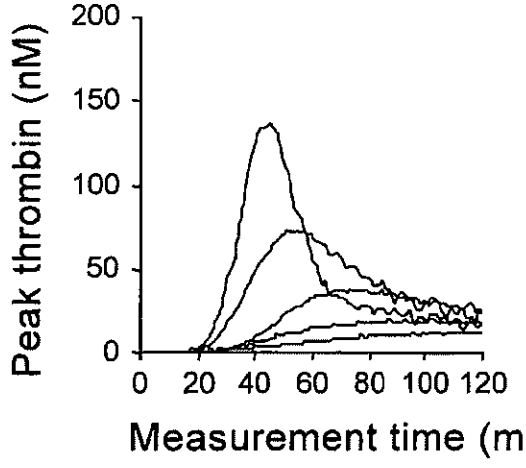


Figure 36E

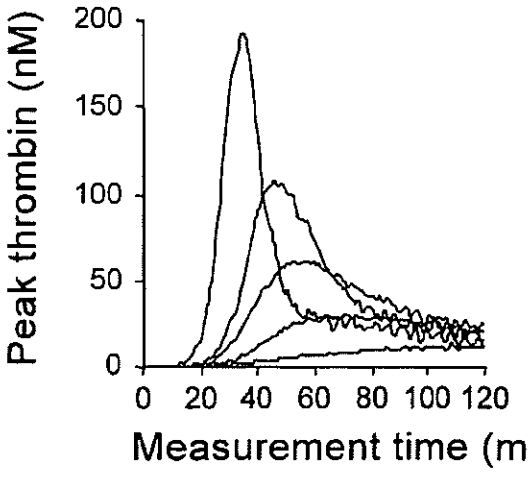


Figure 36F

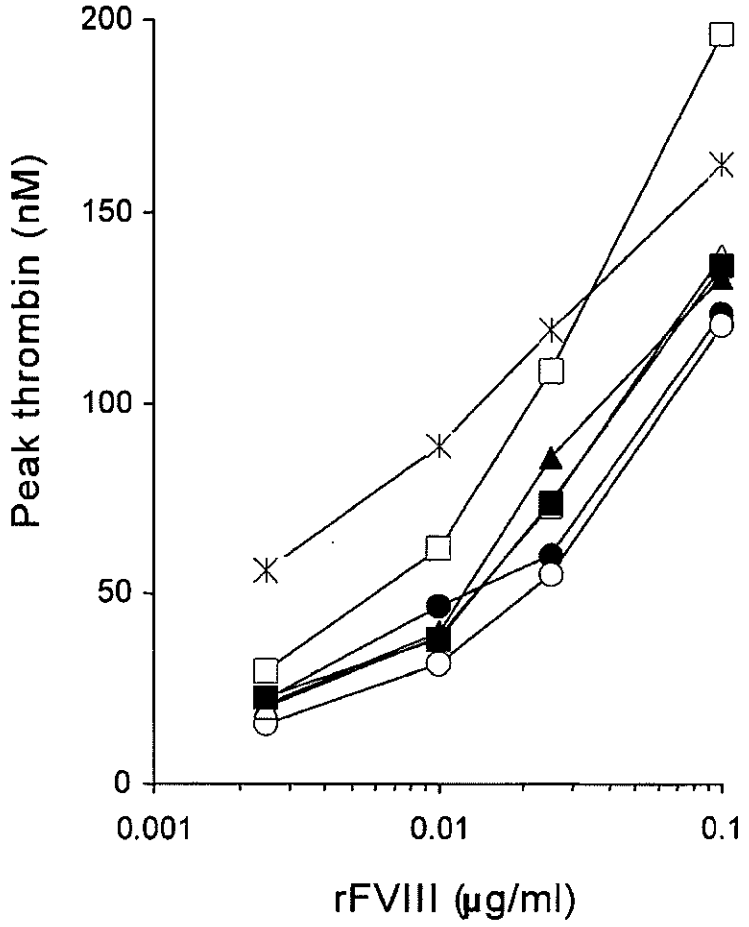


Figure 36G

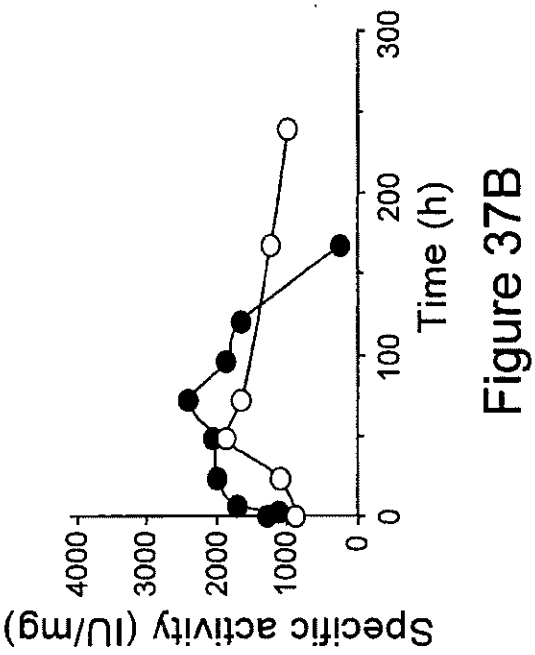


Figure 37B

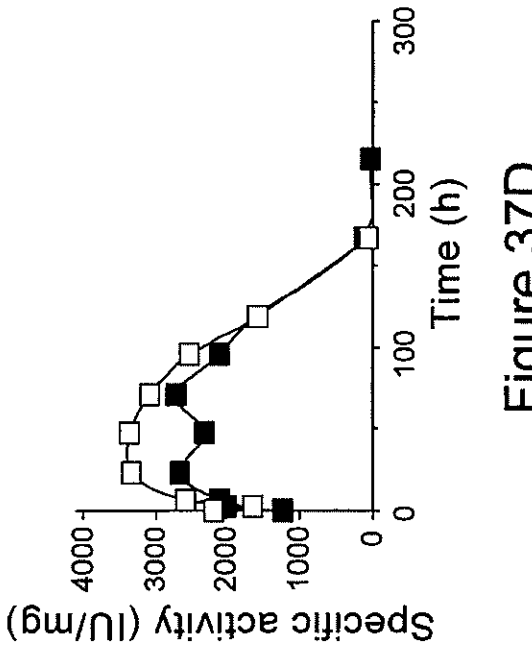


Figure 37D

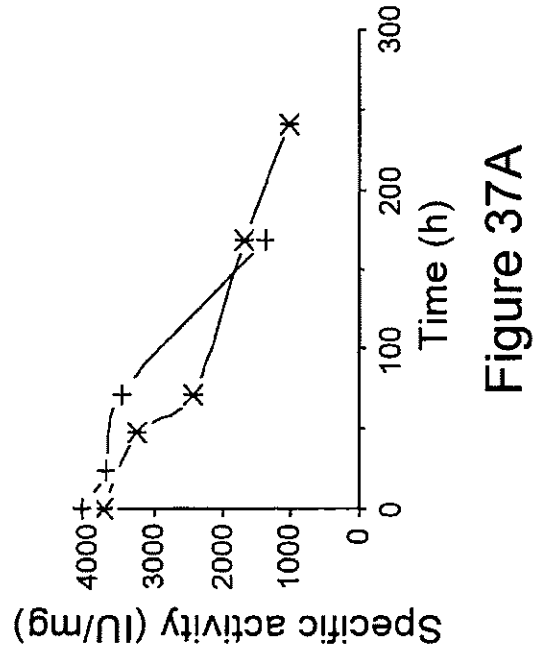


Figure 37A

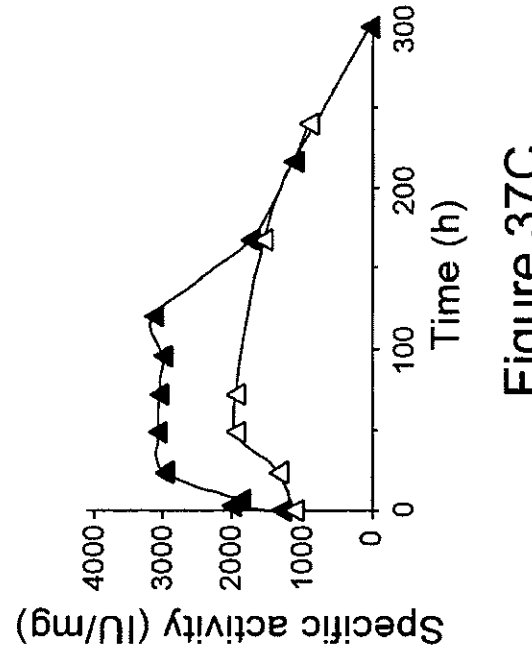


Figure 37C

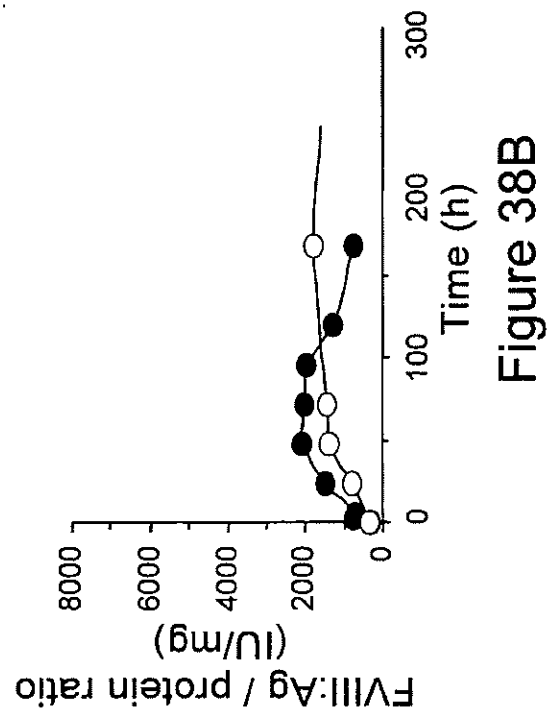


Figure 38B

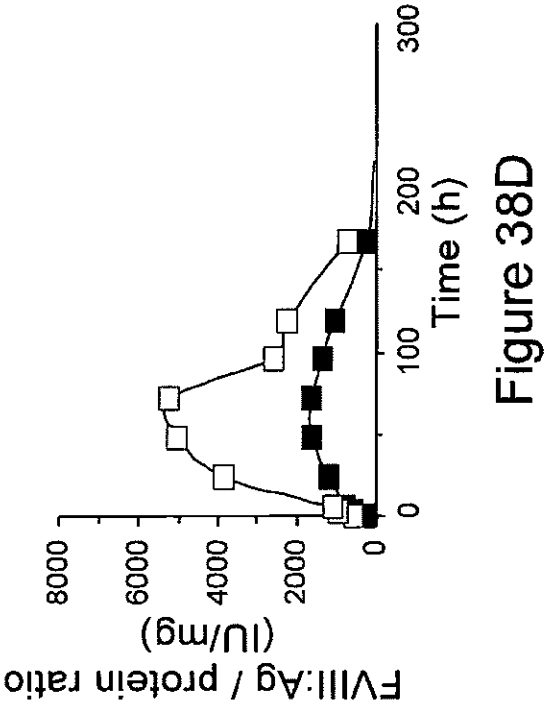


Figure 38D

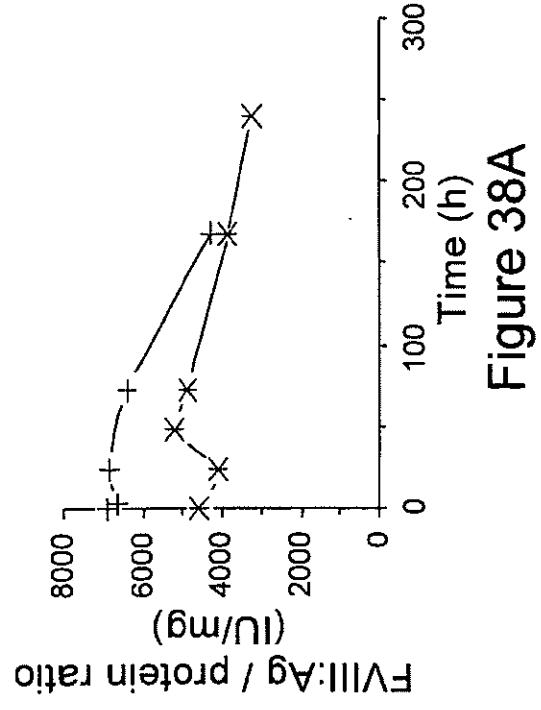


Figure 38A

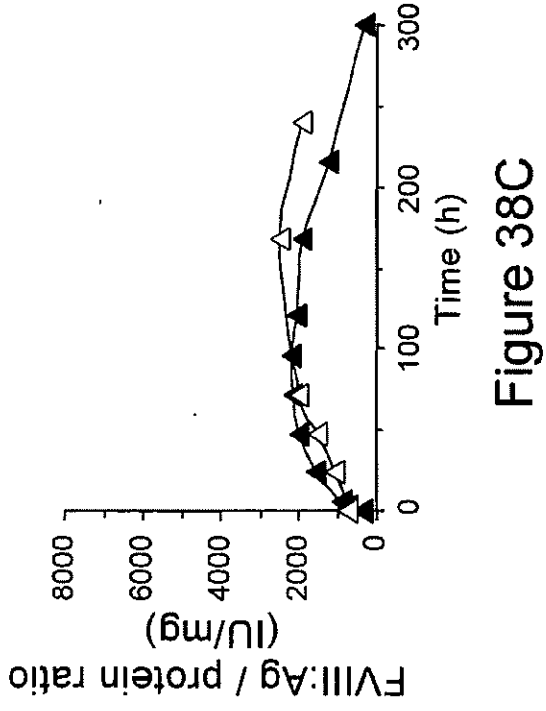


Figure 38C

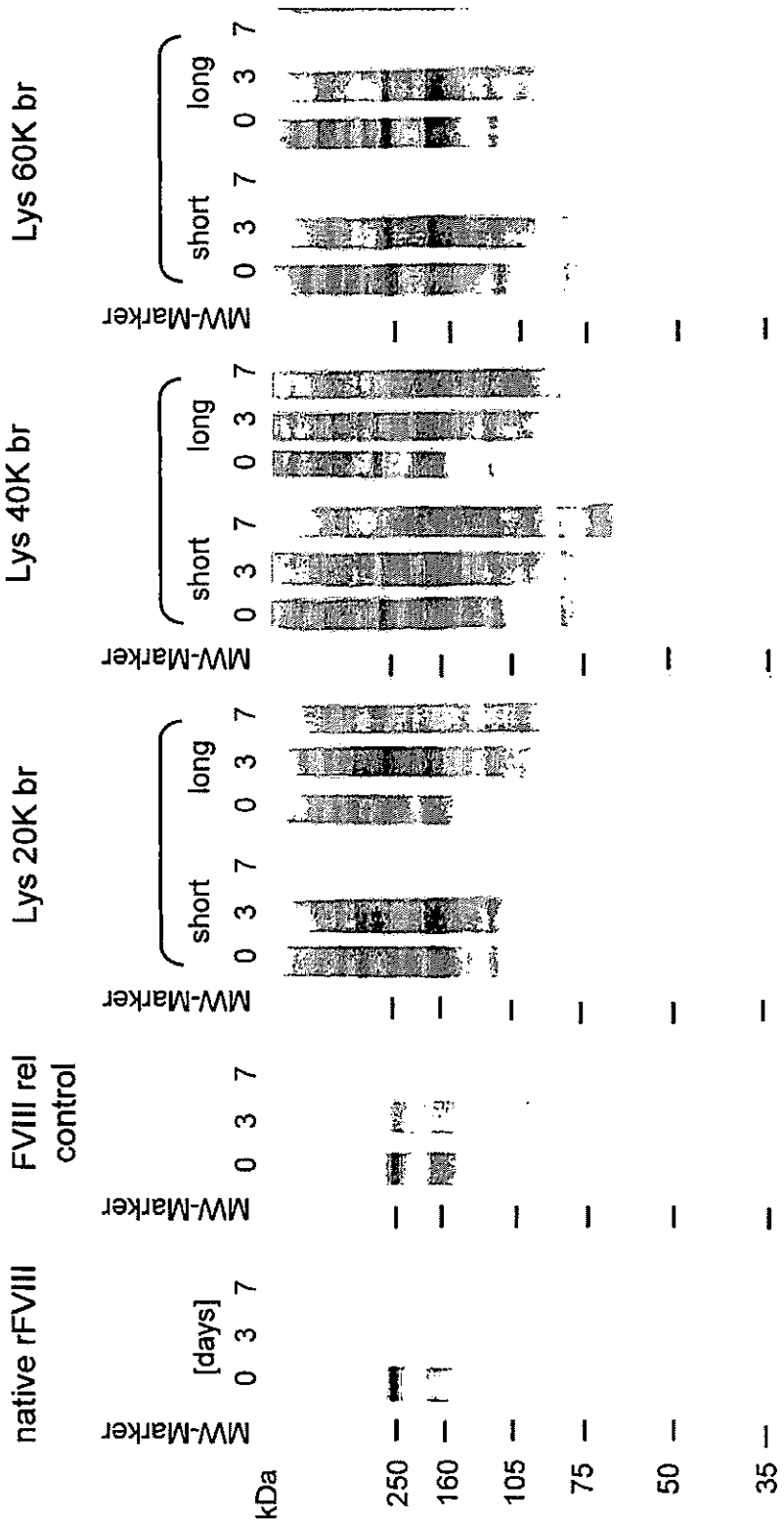

native rFVIII
FVIII rel control
Lys 20K br
Lys 40K br
Lys 60K br
MW-Marker
[days]
0 3 7
short
long
kDa
250
160
105
75
50
35

Figure 39

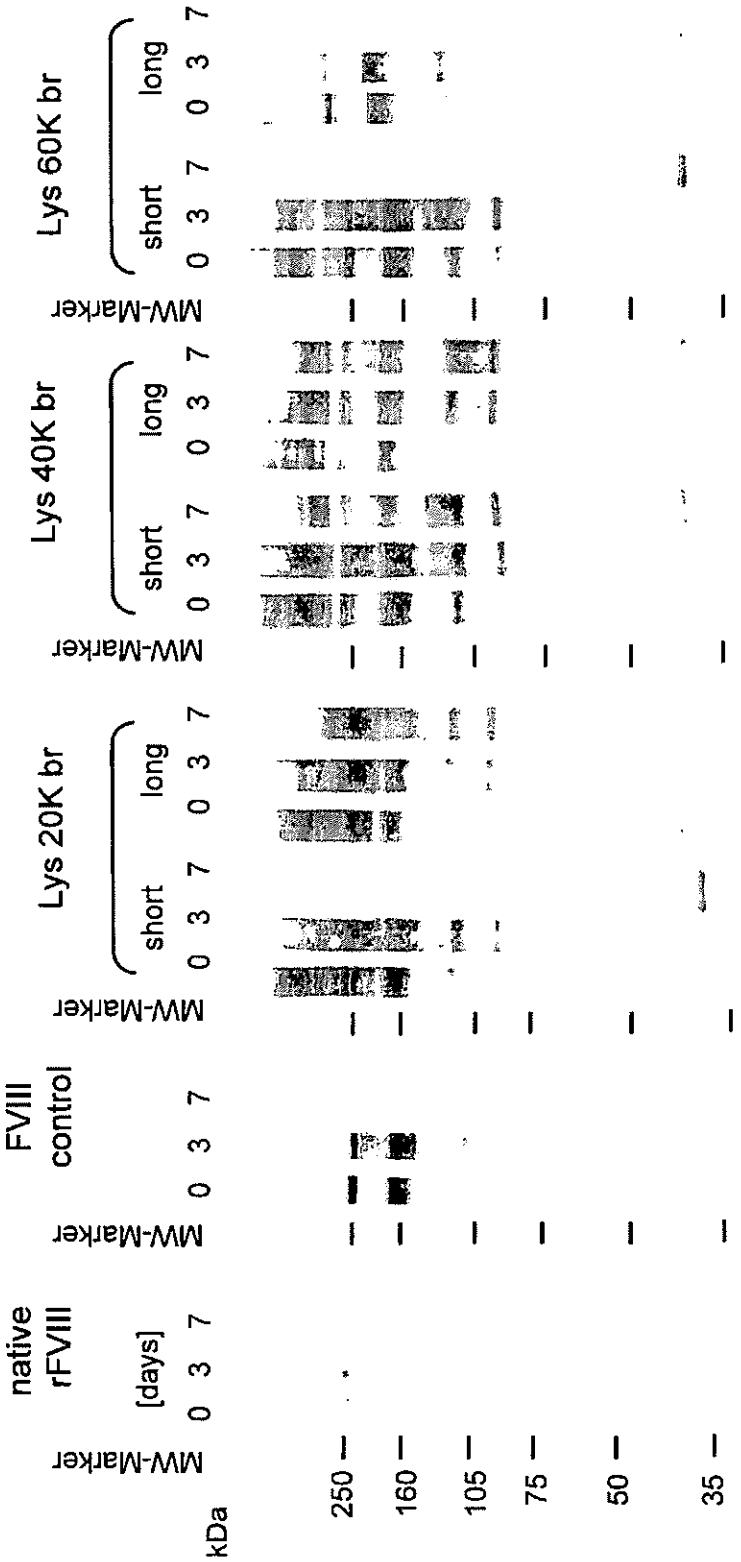

native rFVIII
FVIII control
Lys 20K br
Lys 40K br
Lys 60K br
short
long
[days]
0 3 7
MW-Marker
kDa
250
160
105
75
50
35

Figure 40

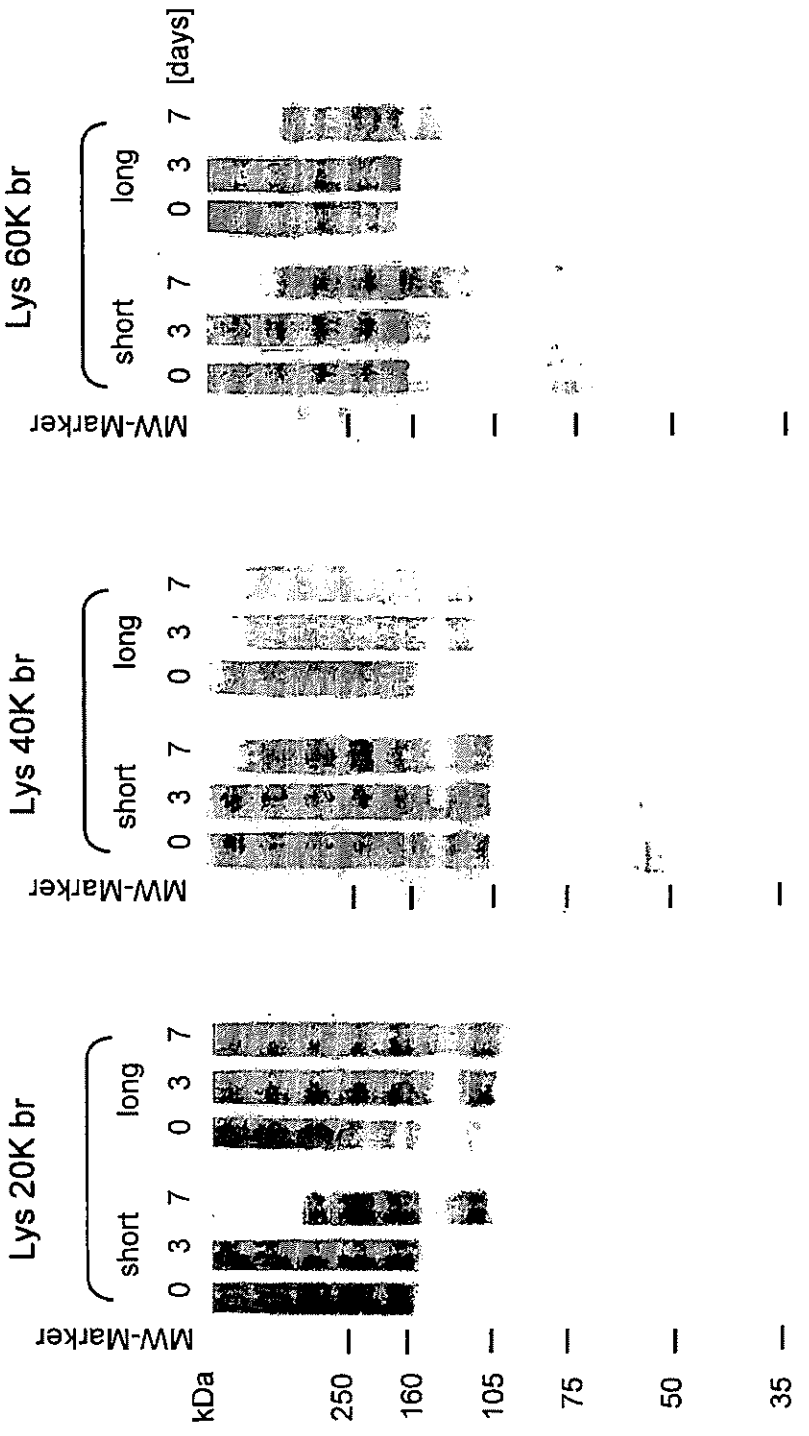

Lys 60K br
Lys 40K br
Lys 20K br
short
long
0 3 7 0 3 7 [days]
MW-Marker
kDa
250
160
105
75
50
35

Figure 41

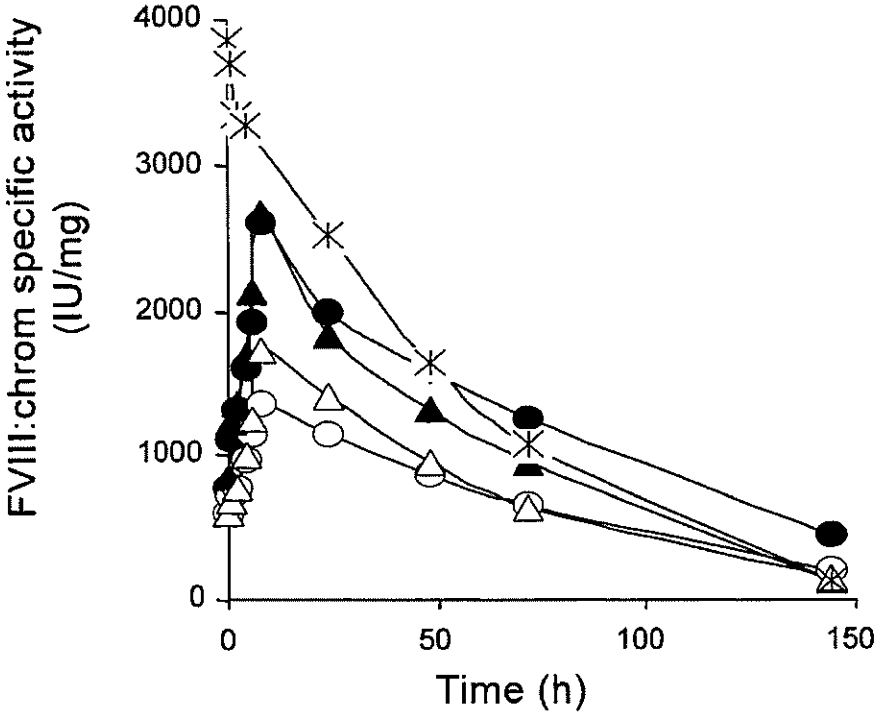


Figure 42A

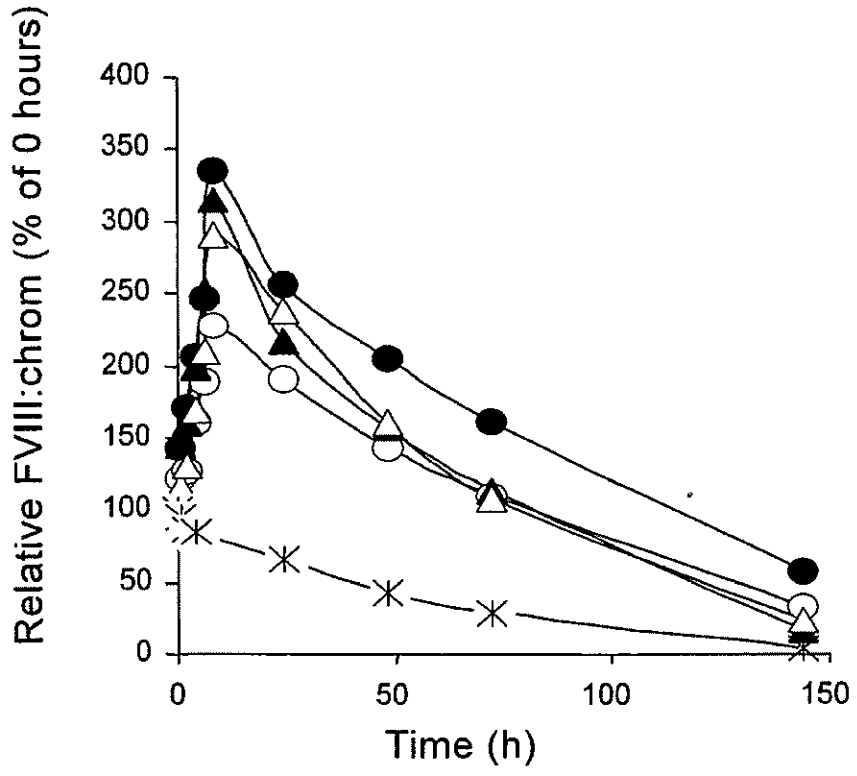


Figure 42B

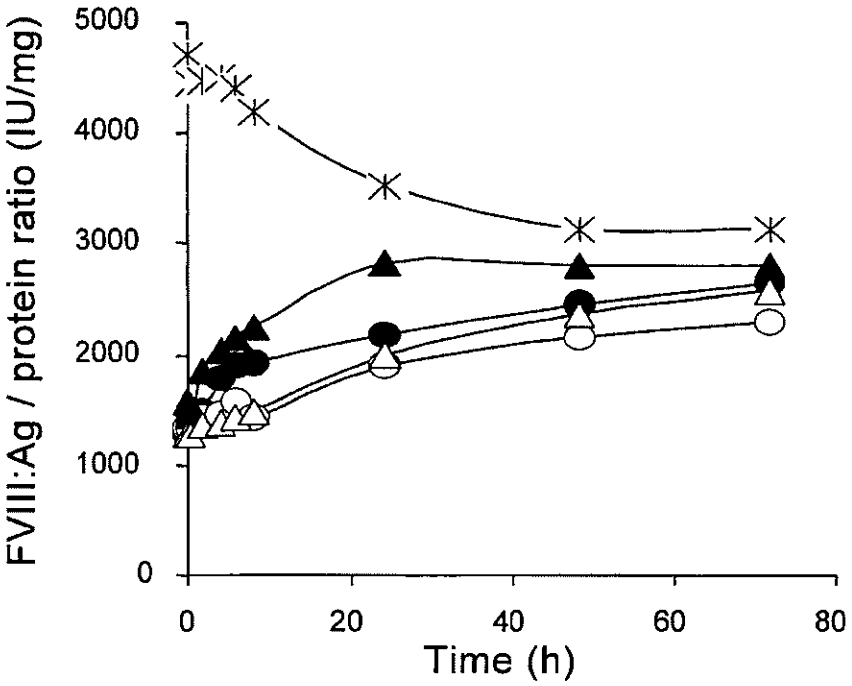


Figure 43A

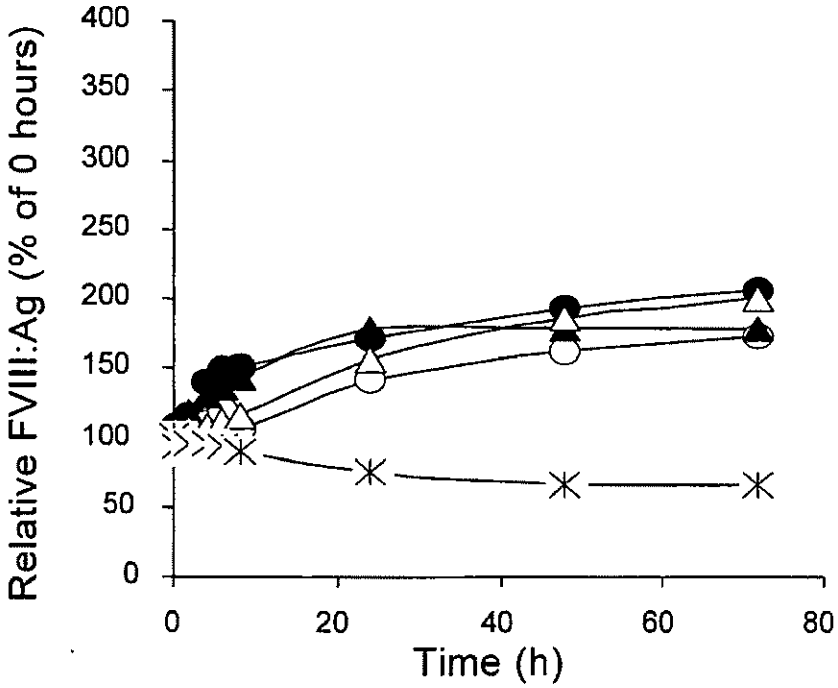


Figure 43B

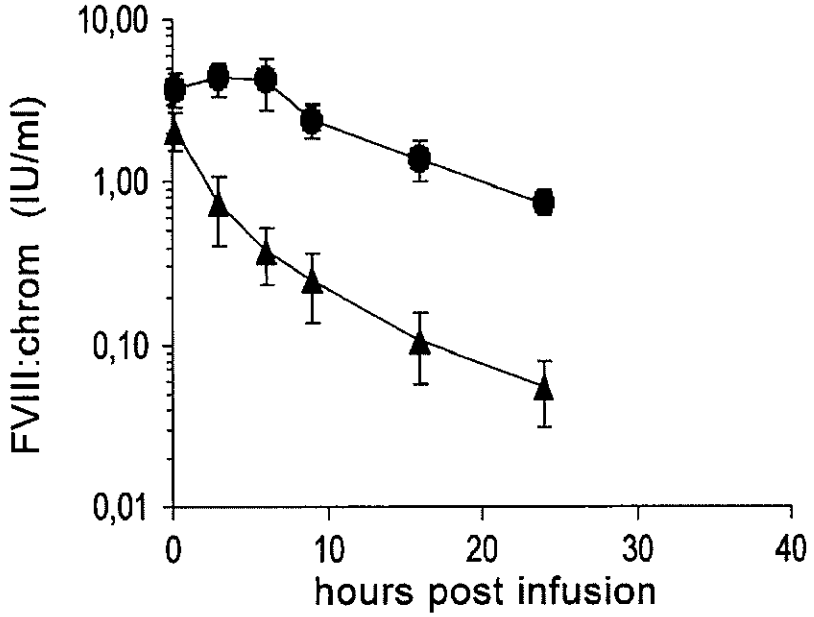


Figure 44A

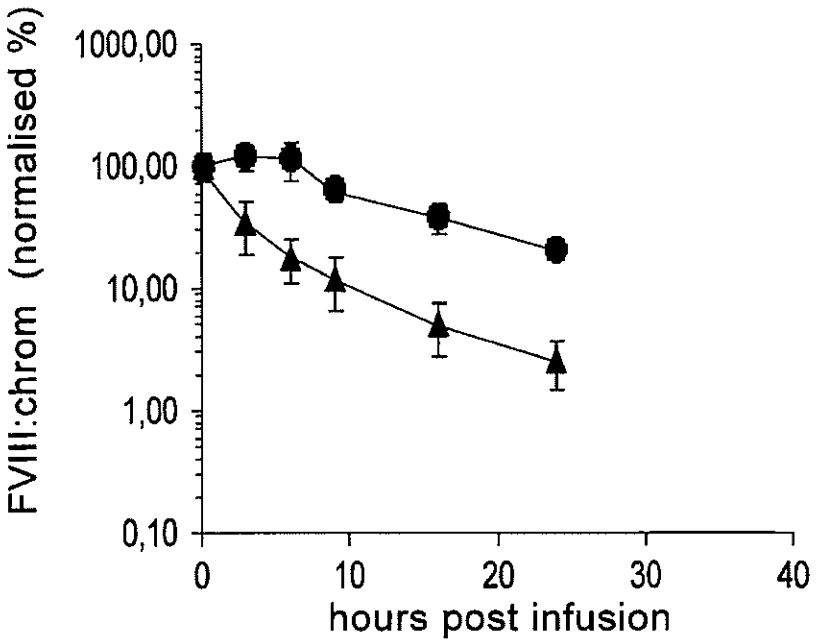


Figure 44B

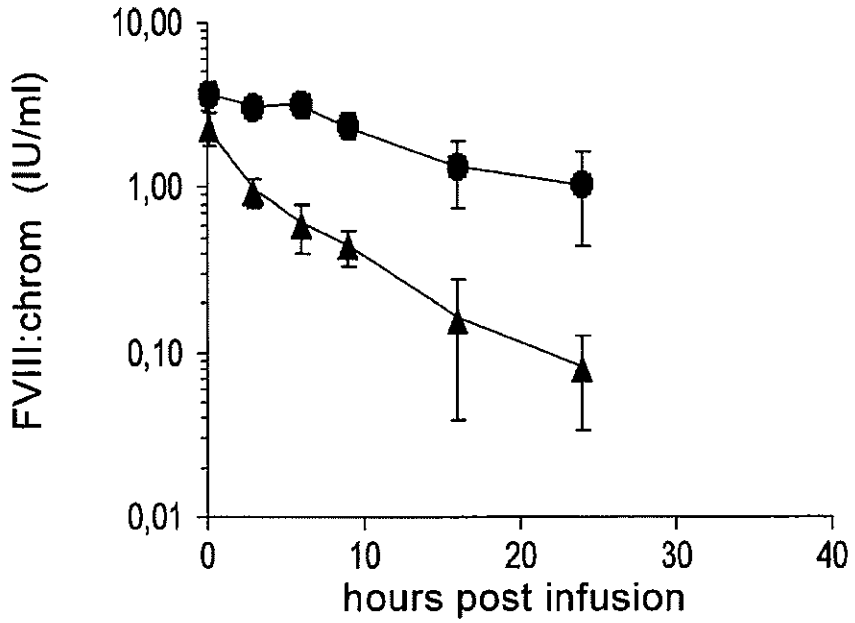


Figure 45A

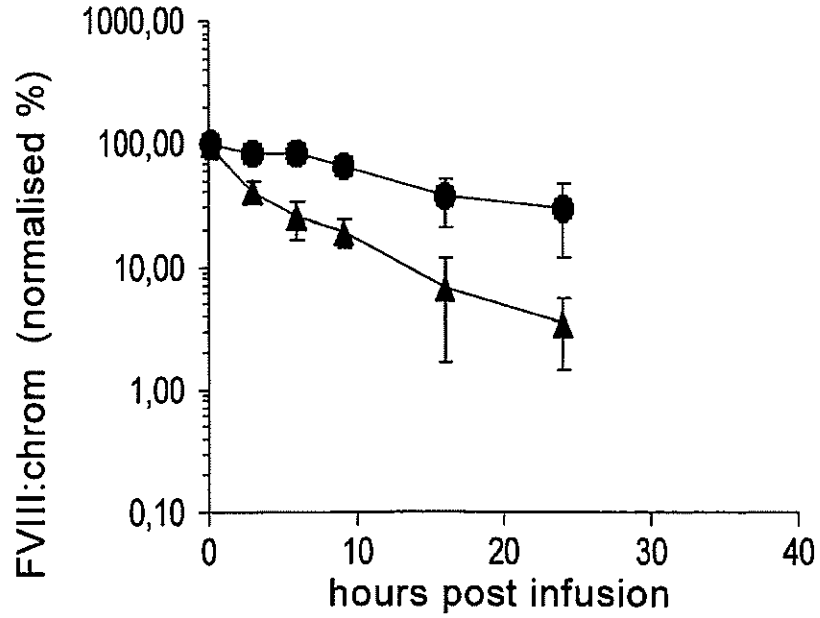


Figure 45B

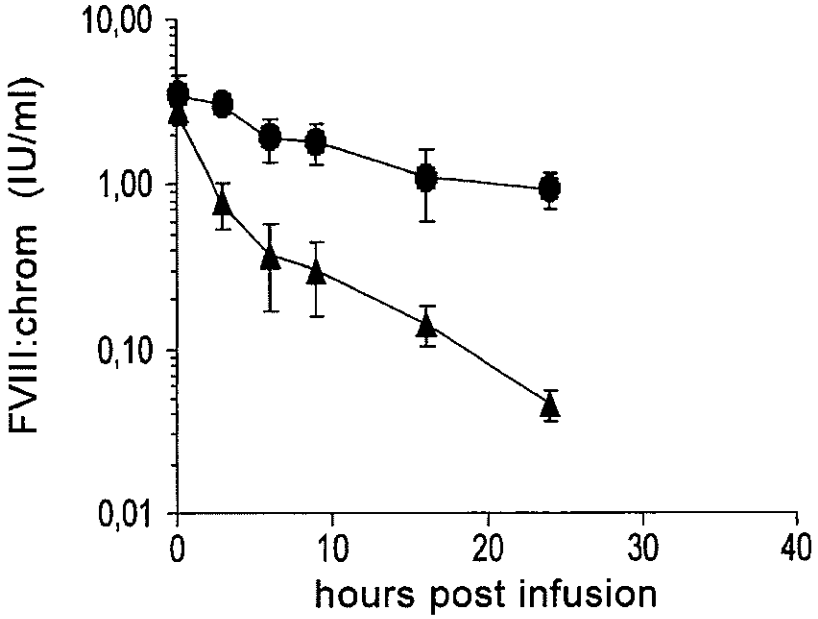


Figure 46A

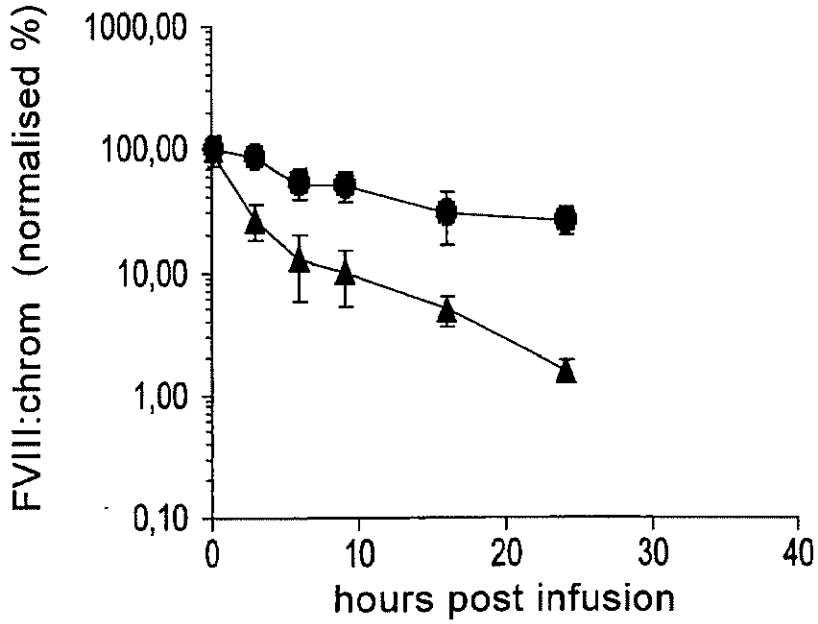


Figure 46B

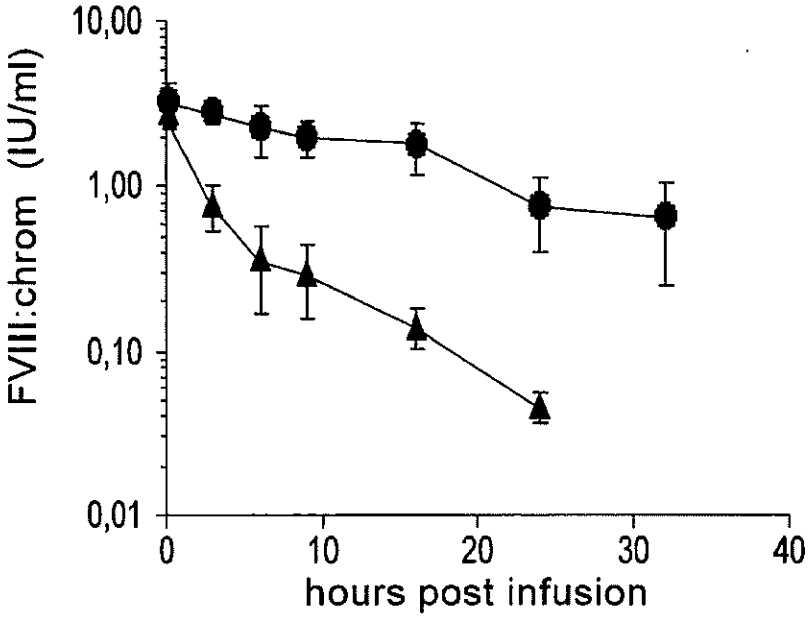


Figure 47A

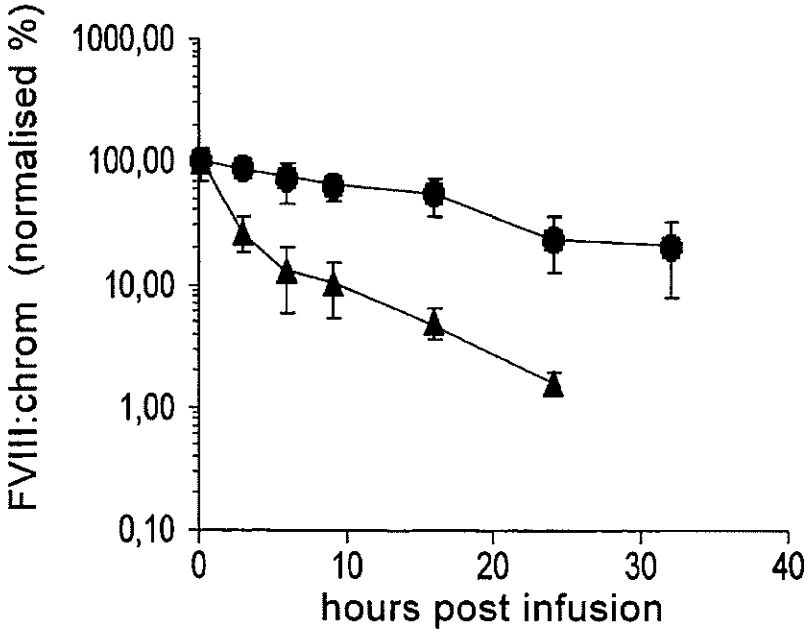


Figure 47B

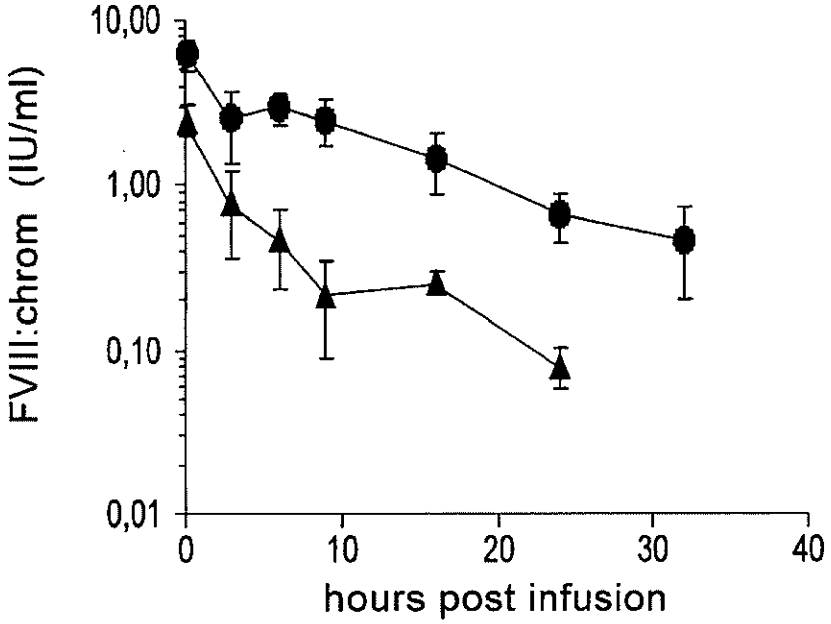


Figure 48A

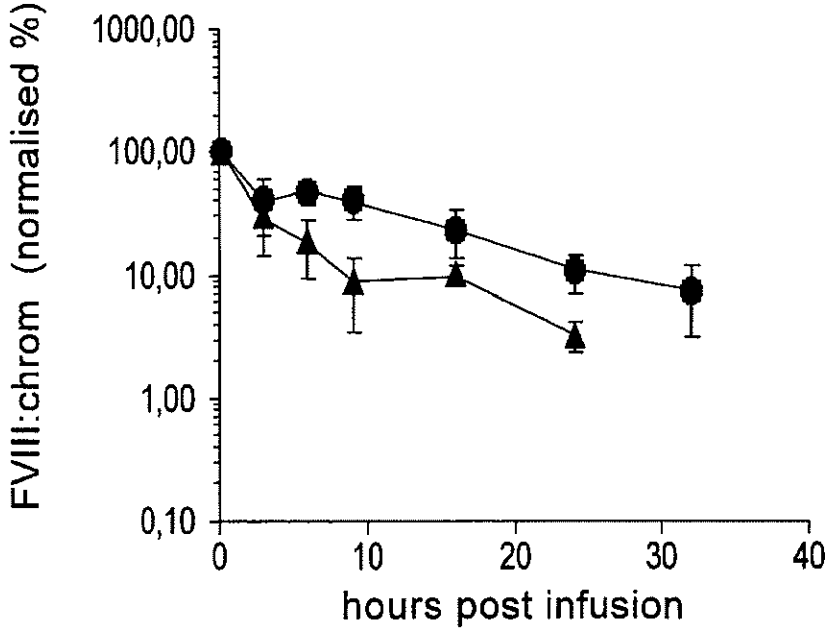


Figure 48B

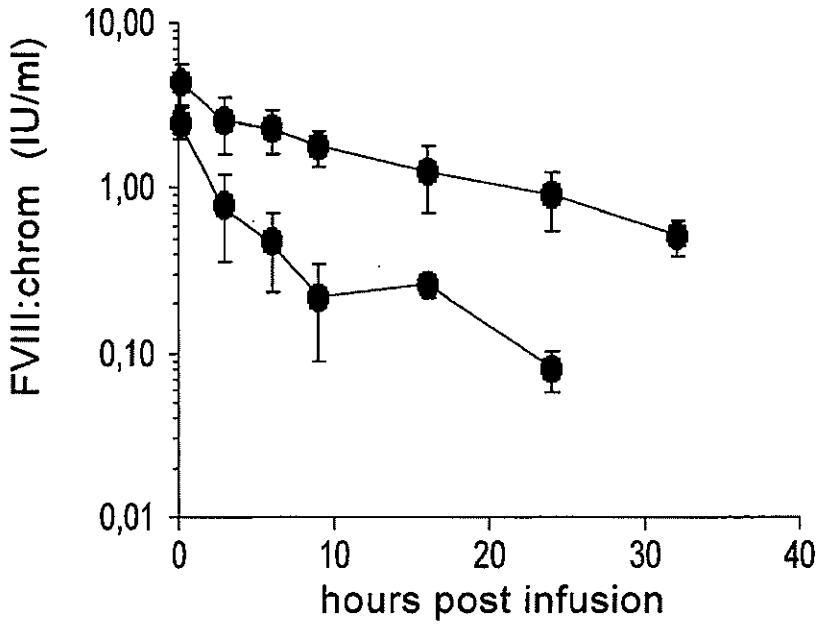


Figure 49A

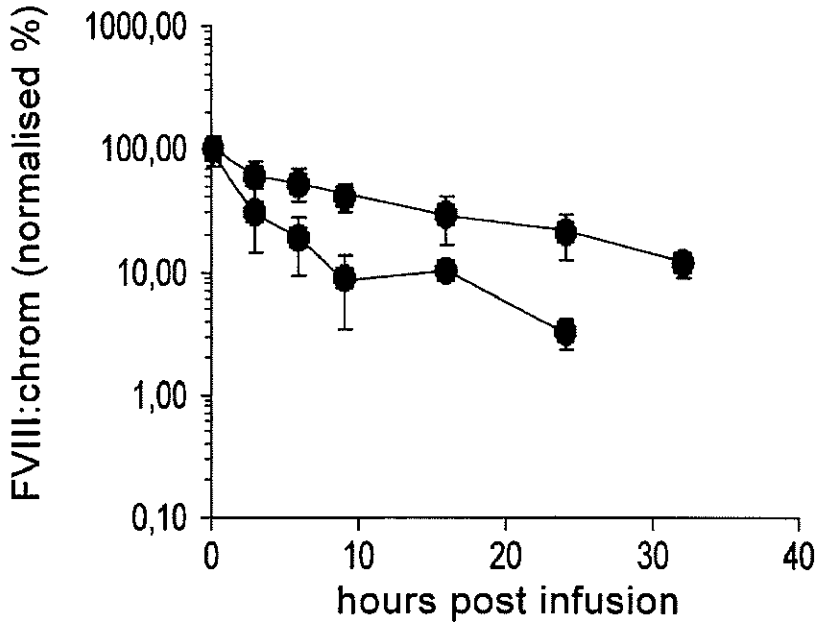


Figure 49B

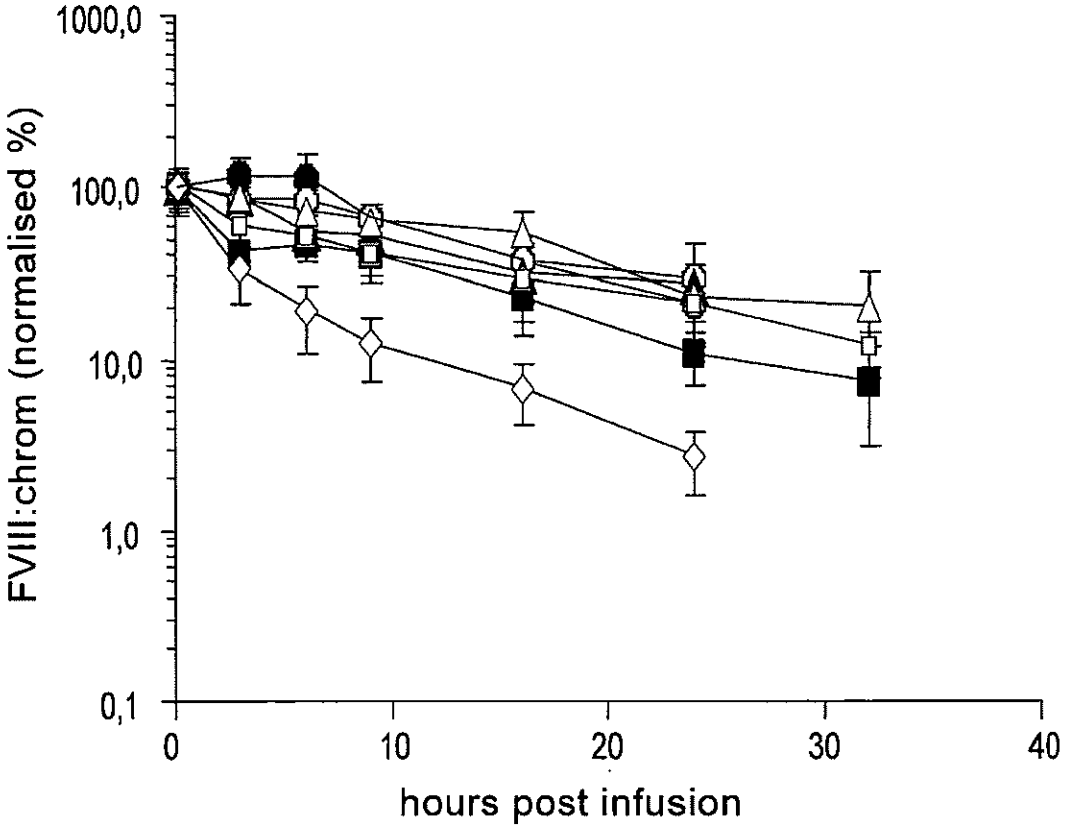

1000,0
100,0
10,0
1,0
0,1
FVIII:chrom (normalised %)
0
10
20
30
40
hours post infusion

Figure 50

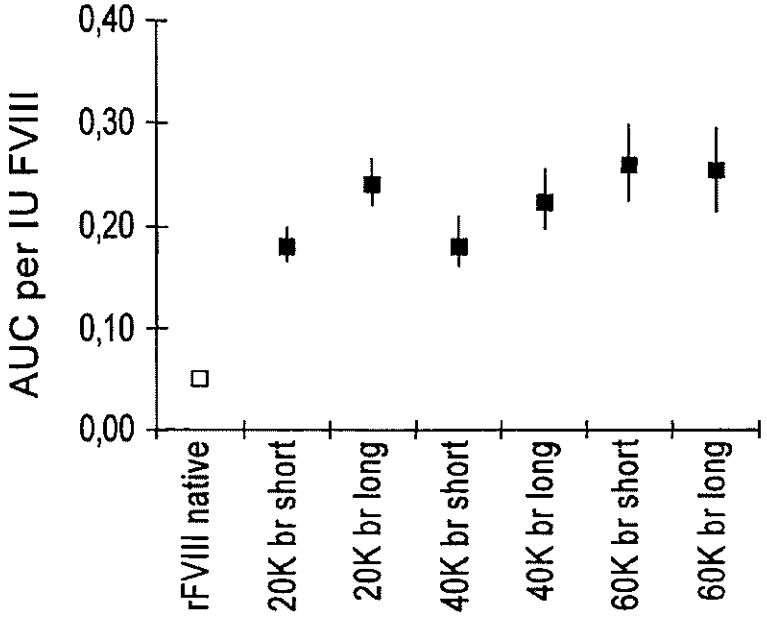


Figure 51A

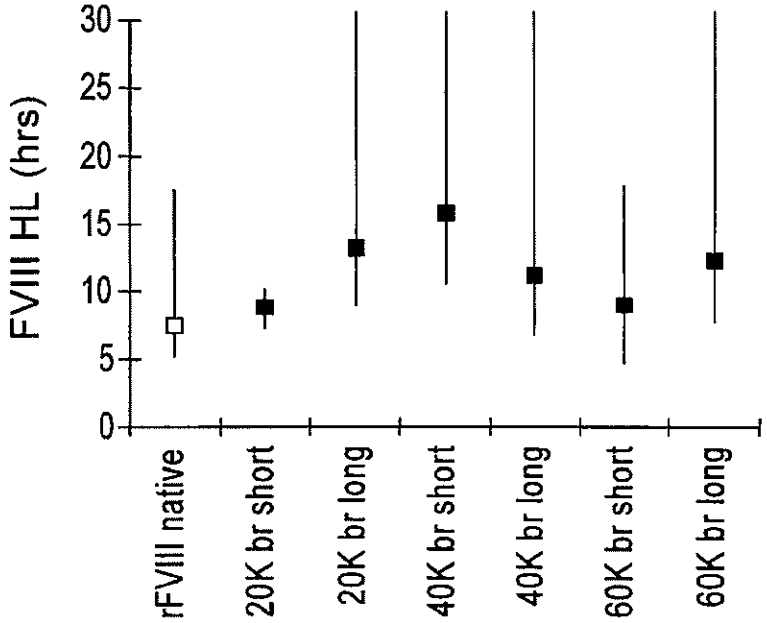


Figure 51B

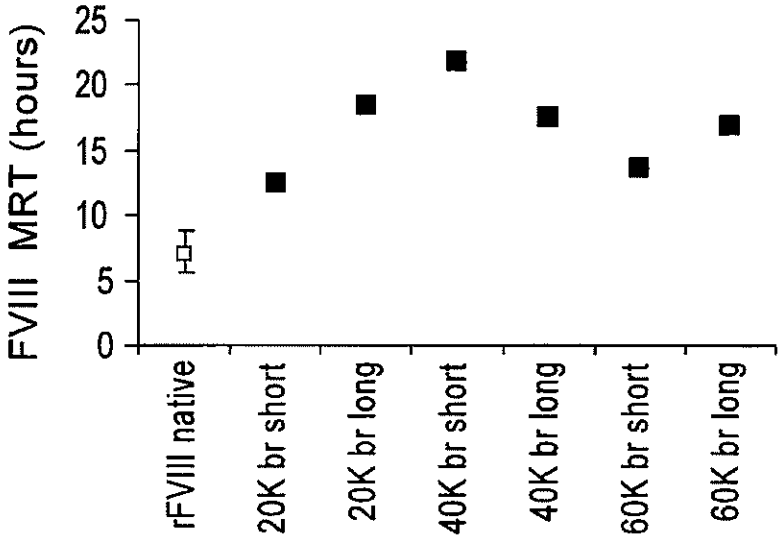

FVIII MRT (hours)
25
20
15
10
5
0
rFVIII native
20K br short
20K br long
40K br short
40K br long
60K br short
60K br long

Figure 52