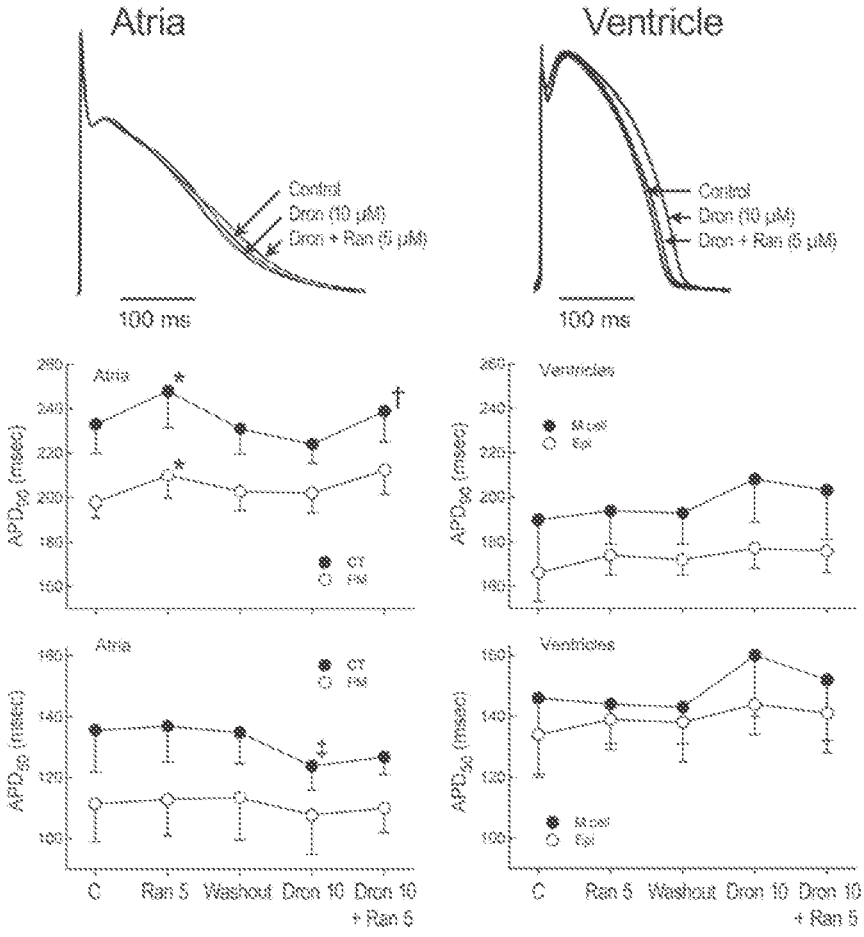

Atria
Ventricle
Control
Dron (10 μM)
Dron + Ran (5 μM)
100 ms
Atria
Ventricles
APD90 (msec)
Ctl
Ran 5
Washout
Dron 10
Dron 10 + Ran 5

Figure 1

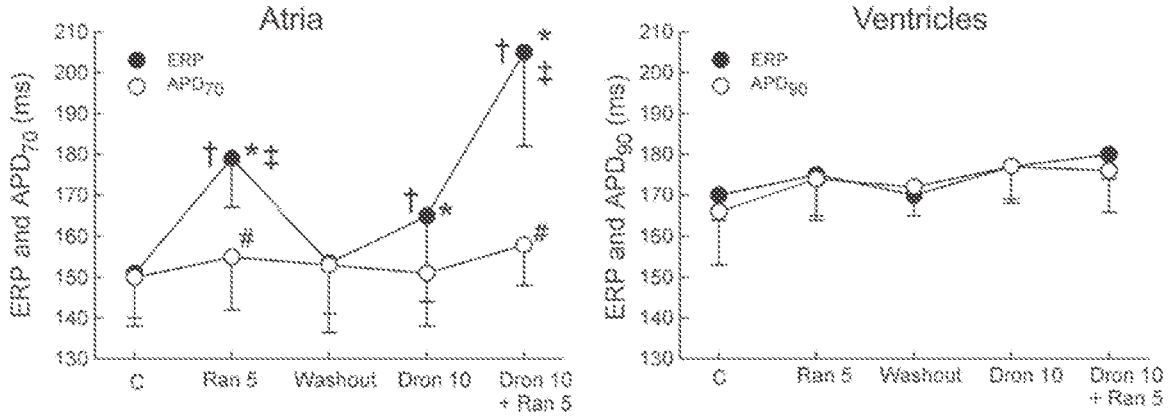


Figure 2

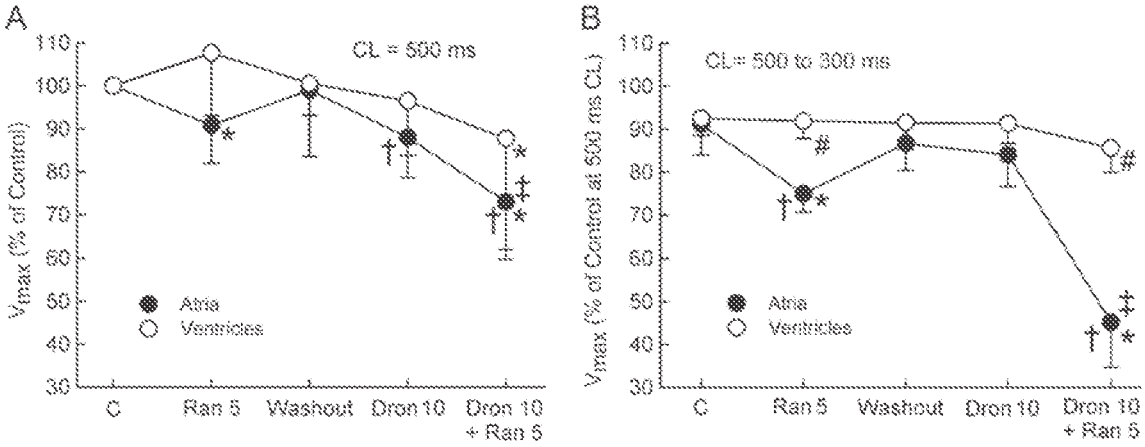


Figure 3

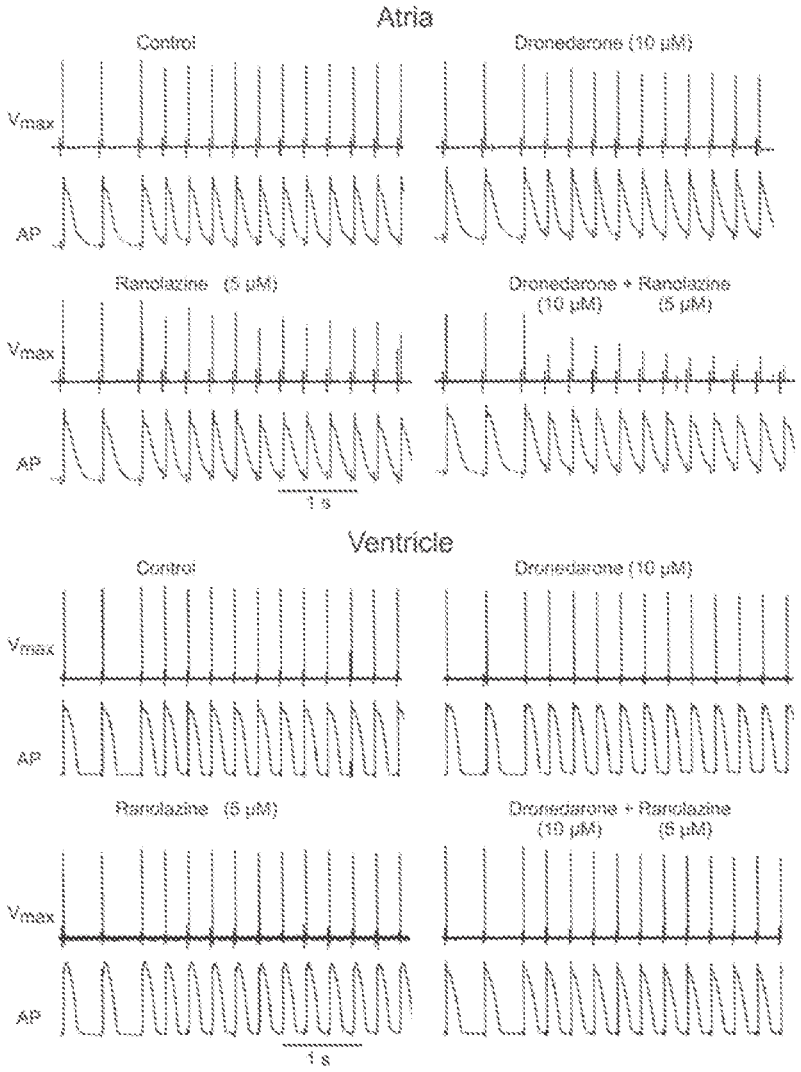

Atria
Control
Dronedarone (10 μM)
Vmax
AP
Ranolazine (5 μM)
Dronedarone + Ranolazine
(10 μM) (5 μM)
Vmax
AP
1 s
Ventricle
Control
Dronedarone (10 μM)
Vmax
AP
Ranolazine (5 μM)
Dronedarone + Ranolazine
(10 μM) (5 μM)
Vmax
AP
1 s

Figure 4

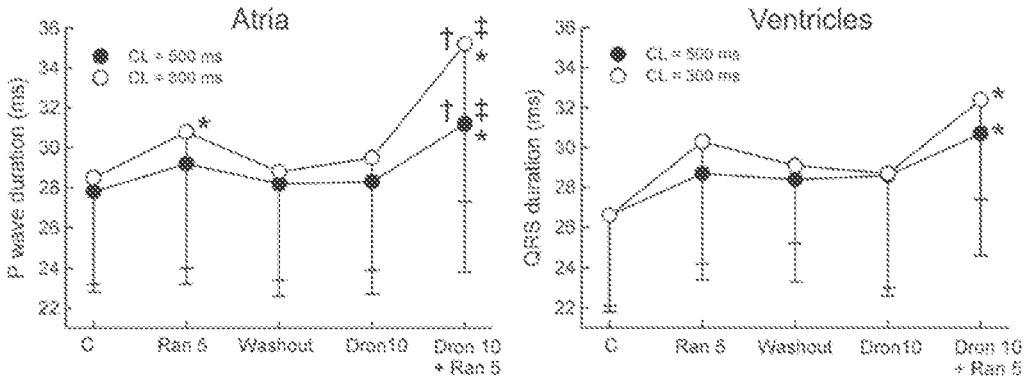


Figure 5

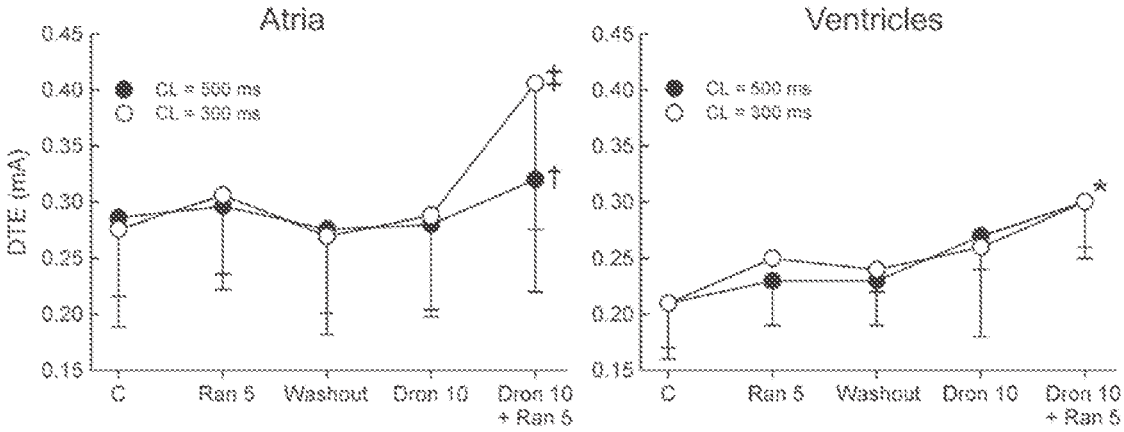


Figure 6

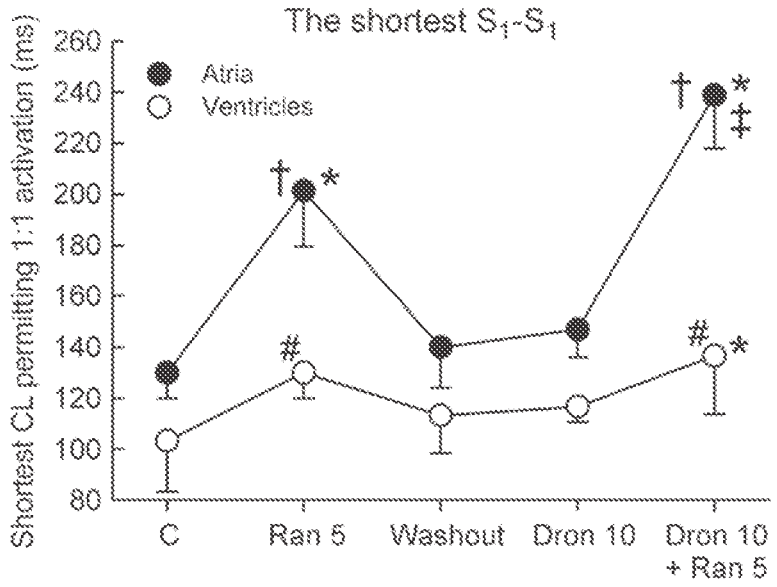

The shortest S_1-S_1
Shortest CL permitting 1:1 activation (ms)
260
240
220
200
180
160
140
120
100
80
Atria
Ventricles
†
*
#
‡
C
Ran 5
Washout
Dron 10
Dron 10 + Ran 5

Figure 7

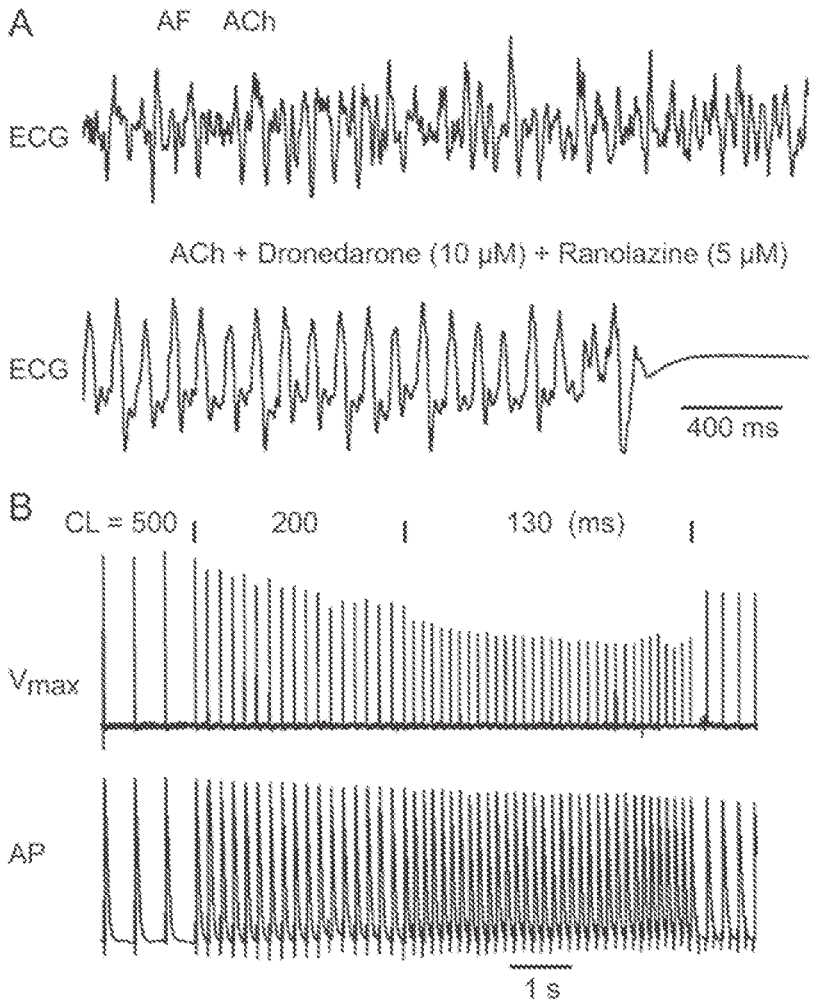

A
AF
ACh
ECG
ACh + Dronedarone (10 μM) + Ranolazine (5 μM)
ECG
400 ms
B
CL = 500
200
130 (ms)
Vmax
AP
1 s

Figure 8

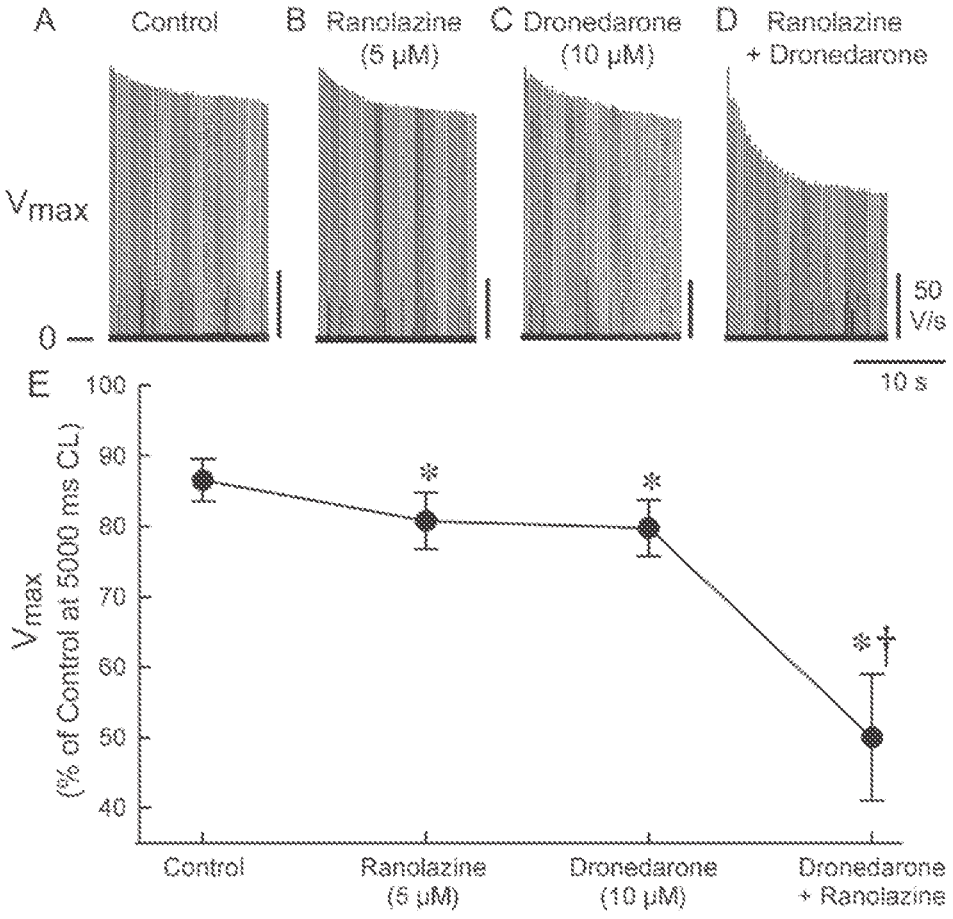

A
Control
B Ranolazine (5 μM)
C Dronedarone (10 μM)
D Ranolazine + Dronedarone
Vmax
0
50 V/s
10 s
E
Vmax (% of Control at 5000 ms CL)
100
90
80
70
60
50
40
*
*
*†
Control
Ranolazine (5 μM)
Dronedarone (10 μM)
Dronedarone + Ranolazine

Figure 9

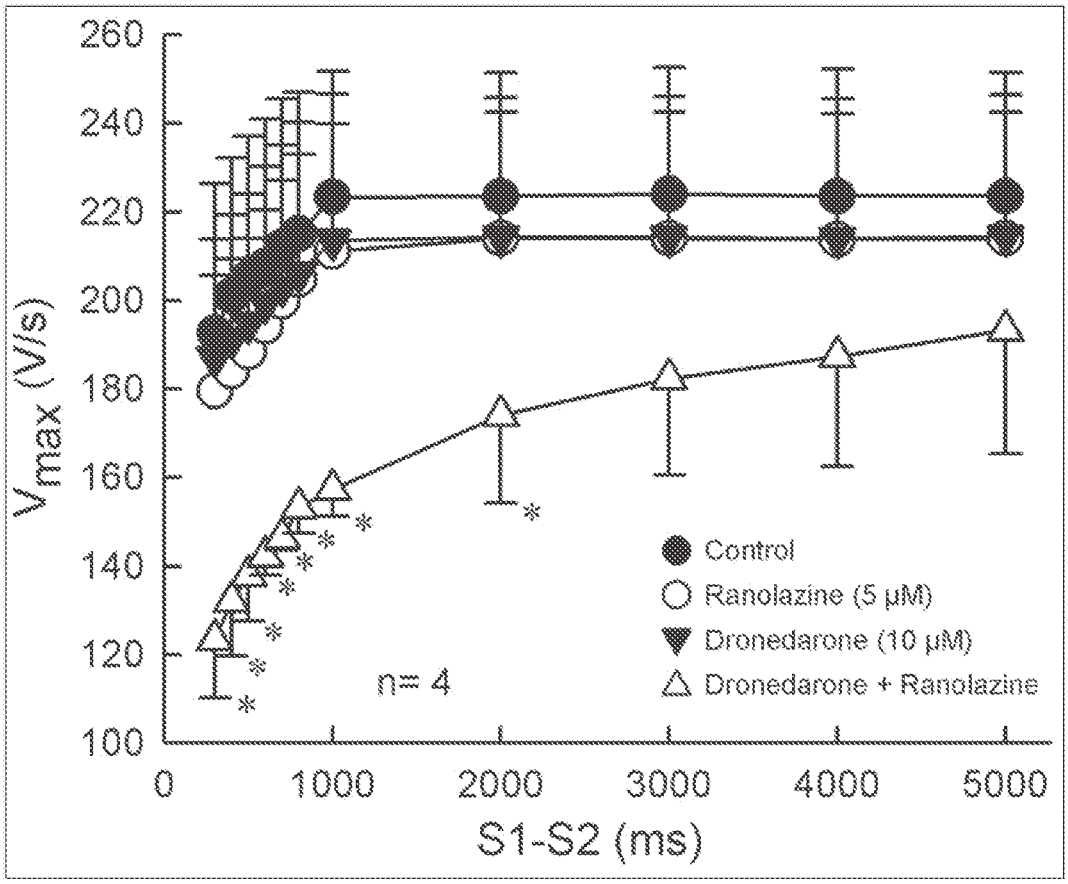

260
240
220
200
180
160
140
120
100
V_{max} (V/s)
0
1000
2000
3000
4000
5000
S1-S2 (ms)
n= 4
Control
Ranolazine (5 μM)
Dronedarone (10 μM)
Dronedarone + Ranolazine

Figure 10

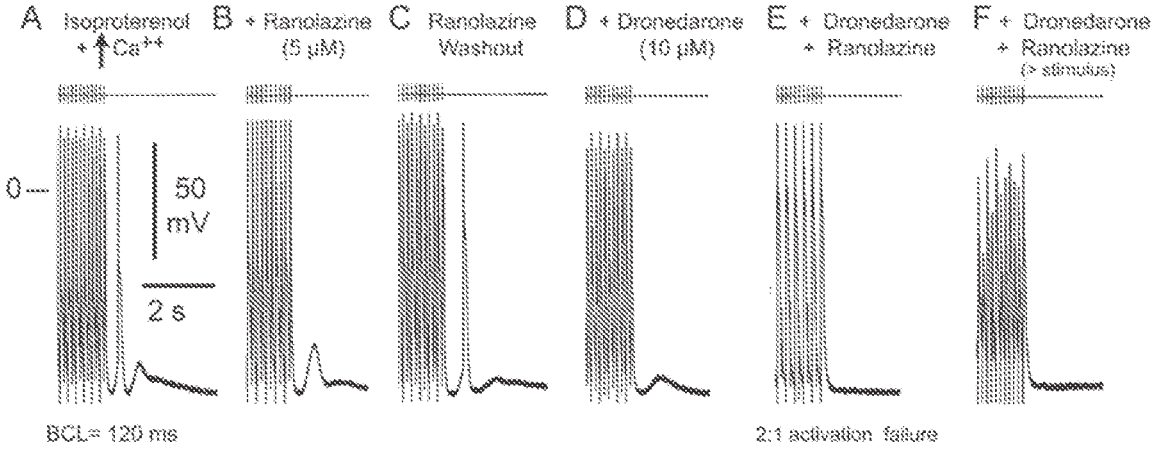


Figure 11

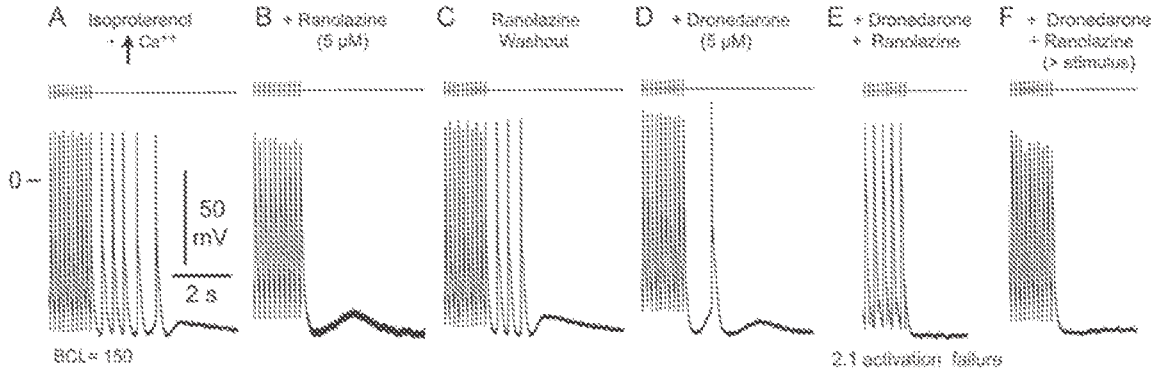


Figure 12

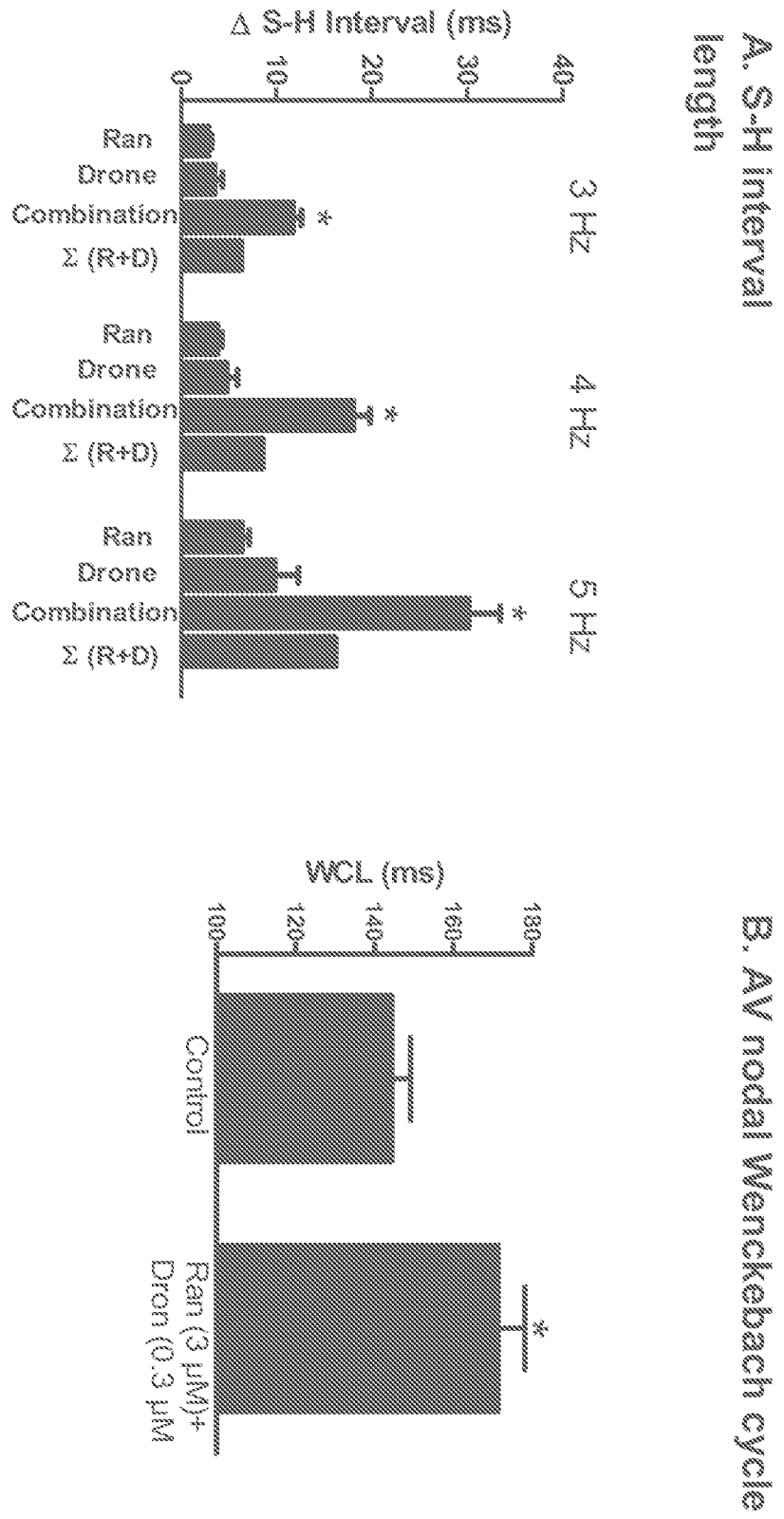

A. S-H Interval length
Δ S-H Interval (ms)
0
10
20
30
40
Ran
Drone
Combination
Σ (R+D)
3 Hz
4 Hz
5 Hz
*
B. AV nodal Wenckebach cycle
WCL (ms)
100
120
140
160
180
Control
Ran (3 μM)+
Dron (0.3 μM
*

Figure 13

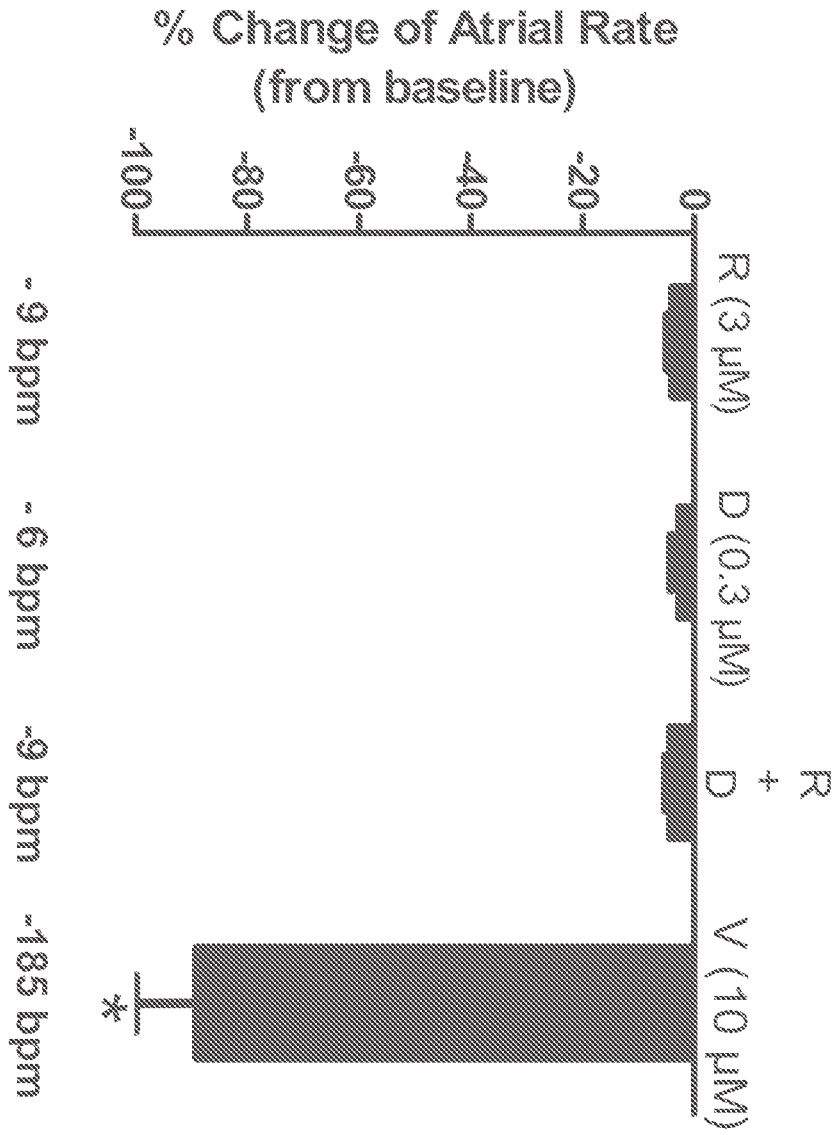

% Change of Atrial Rate
(from baseline)
100
80
60
40
20
0
R (3 uM)
D (0.3 uM)
D + R
V (10 uM)
*
185 bpm
9 bpm
6 bpm
9 bpm

Figure 14

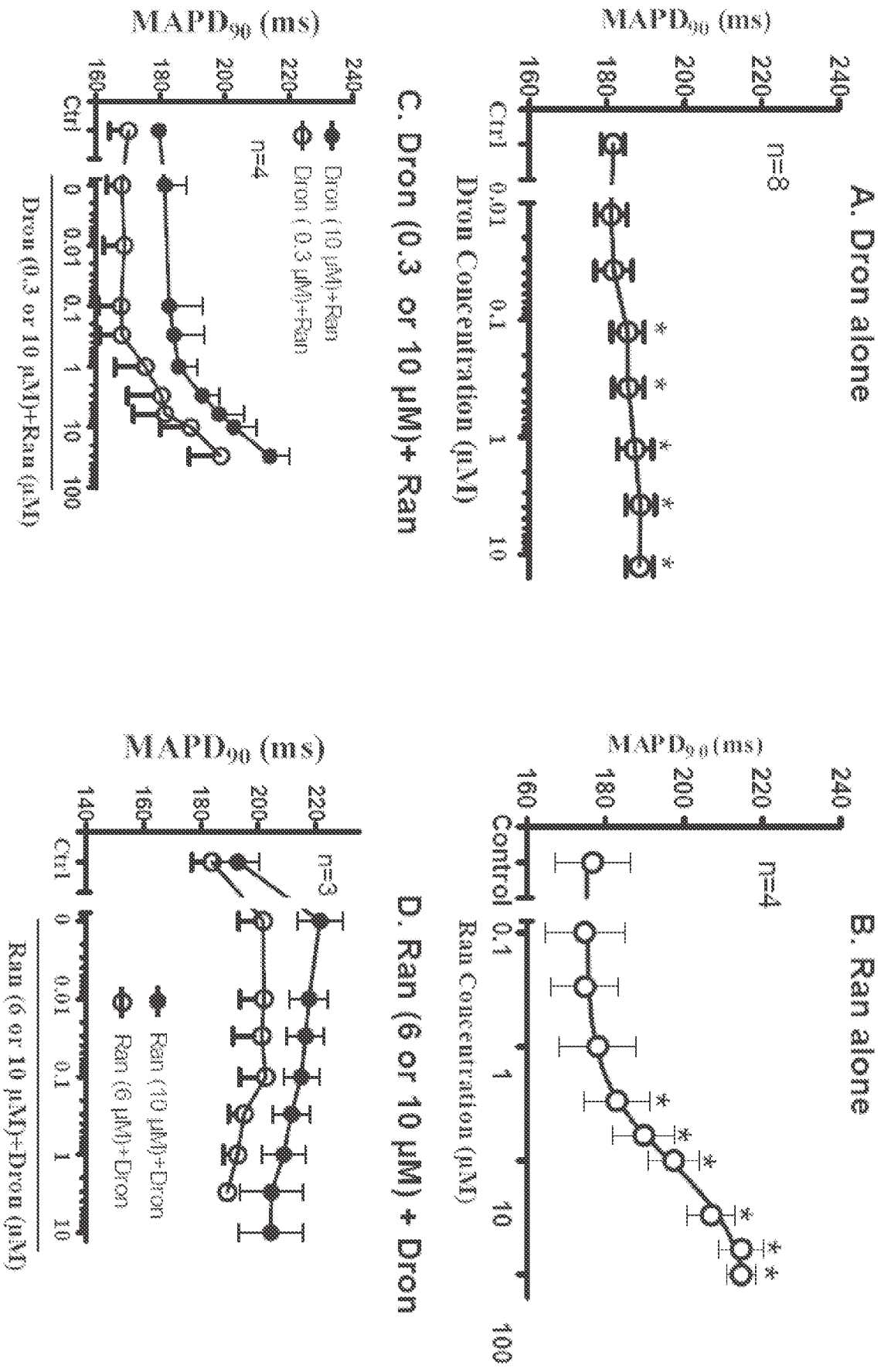

A. Dron alone
MAPD90 (ms)
n=8
Ctrl
Dron Concentration (nM)
B. Ran alone
MAPD90 (ms)
n=4
Control
Ran Concentration (μM)
C. Dron (0.3 or 10 μM)+ Ran
MAPD90 (ms)
n=4
Dron (10 μM)+Ran
Dron (0.3 μM)+Ran
Dron (0.3 or 10 μM)+Ran (μM)
D. Ran (6 or 10 μM) + Dron
MAPD90 (ms)
n=3
Ctrl
Ran (10 μM)+Dron
Ran (6 μM)+Dron
Ran (6 or 10 μM)+Dron (μM)

Figure 15

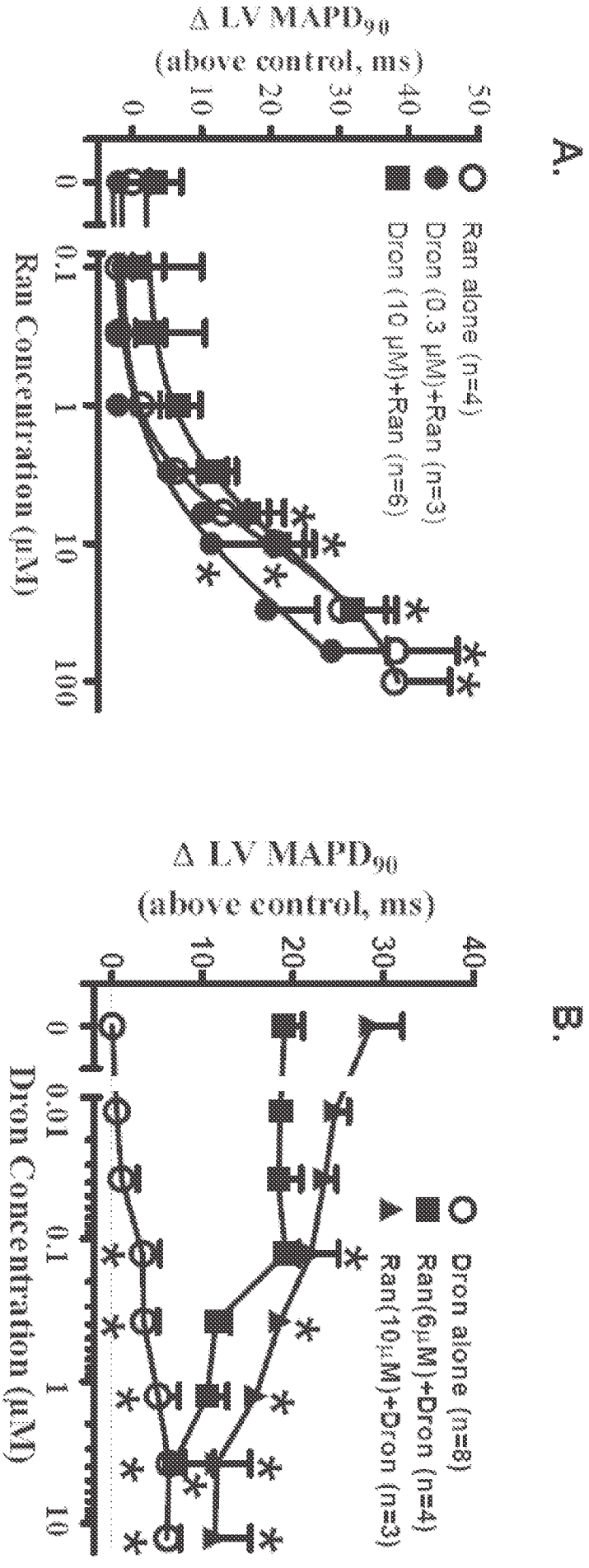

A.
Δ LV MAPD90
(above control, ms)
0
10
20
30
40
50
Ran alone (n=4)
Dron (0.3 μM)+Ran (n=3)
Dron (10 μM)+Ran (n=6)
Ran Concentration (μM)
0
0.1
1
10
100
B.
Δ LV MAPD90
(above control, ms)
0
10
20
30
40
Dron alone (n=8)
Ran(6μM)+Dron (n=4)
Ran(10μM)+Dron (n=3)
Dron Concentration (μM)
0
0.01
0.1
1
10

Figure 16

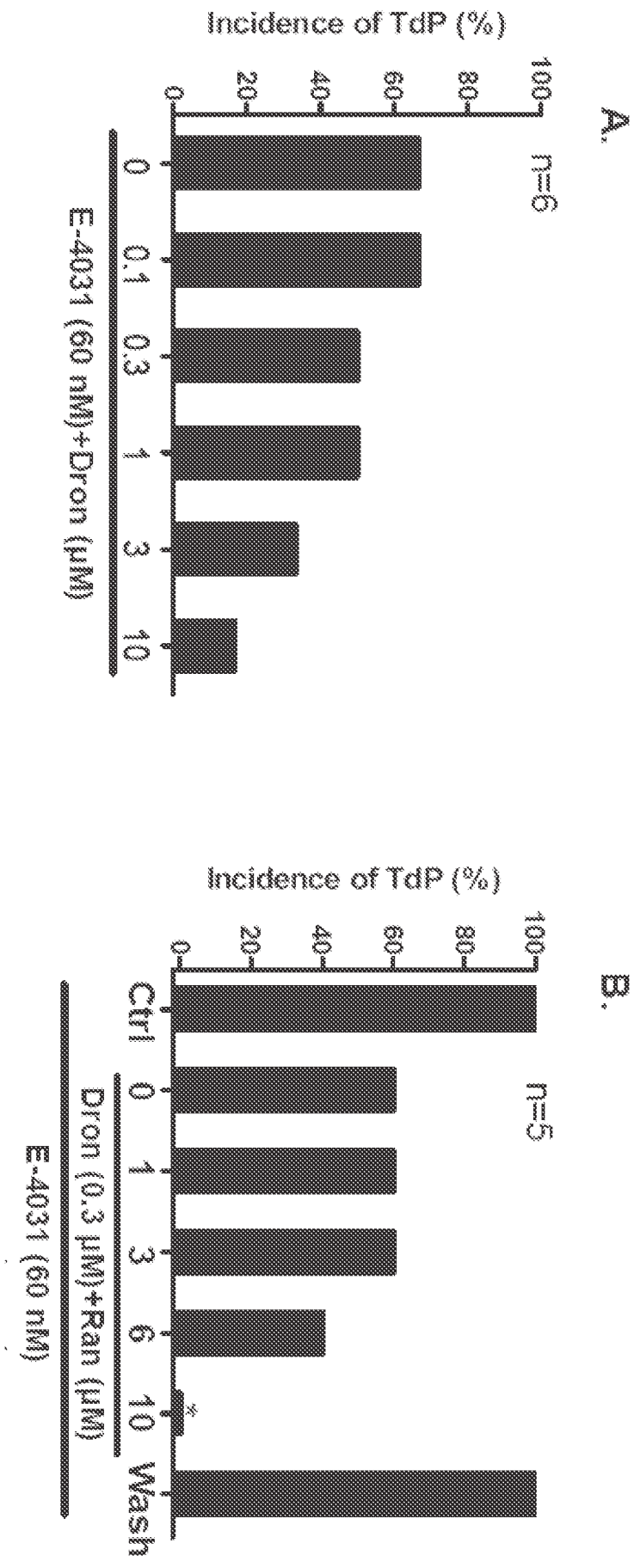

A.
Incidence of TdP (%)
0
20
40
60
80
100
n=6
E-4031 (60 nM)+Dron (μM)
0
0.1
0.3
1
3
10
B.
Incidence of TdP (%)
0
20
40
60
80
100
n=5
E-4031 (60 nM)
Dron (0.3 μM)+Ran (μM)
Ctrl
0
1
3
6
10
Wash
*

Figure 17

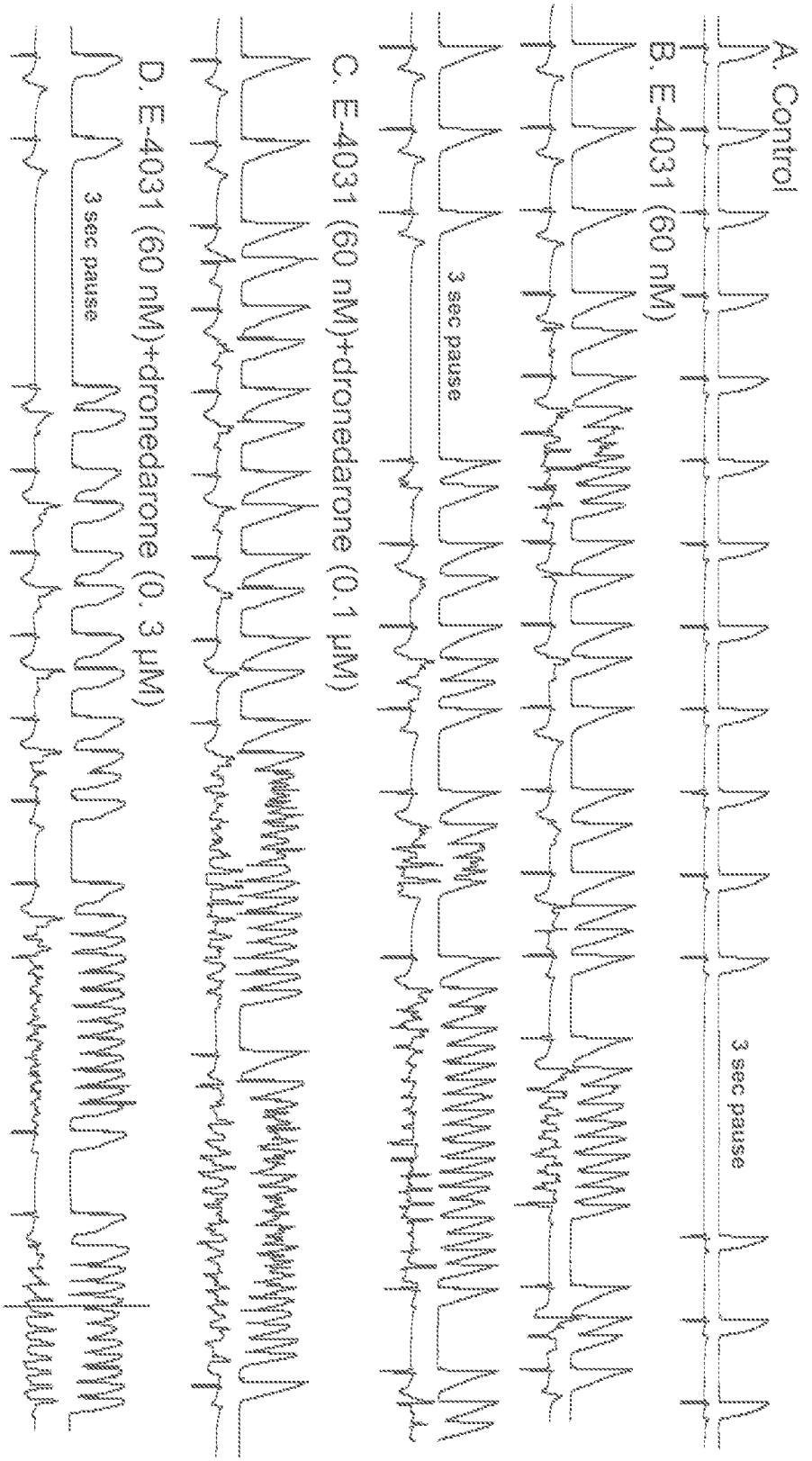

A. Control
3 sec pause
B. E-4031 (60 nM)
3 sec pause
C. E-4031 (60 nM)+dronedarone (0.1 μM)
D. E-4031 (60 nM)+dronedarone (0.3 μM)
3 sec pause

Figure 18

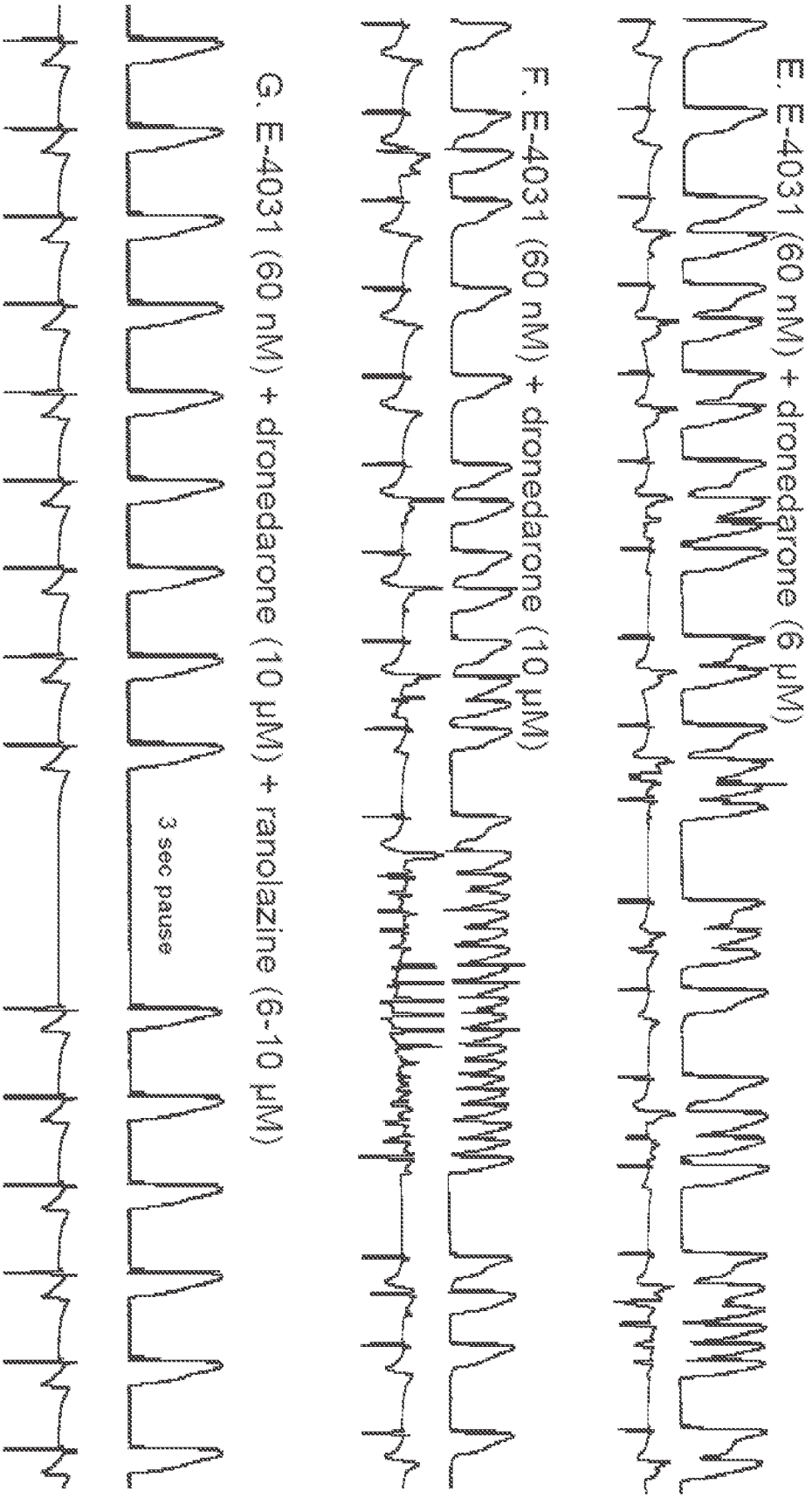

E. E-4031 (60 nM) + dronedarone (6 μM)
F. E-4031 (60 nM) + dronedarone (10 μM)
G. E-4031 (60 nM) + dronedarone (10 μM) + ranolazine (6-10 μM)
3 sec pause

Figure 19

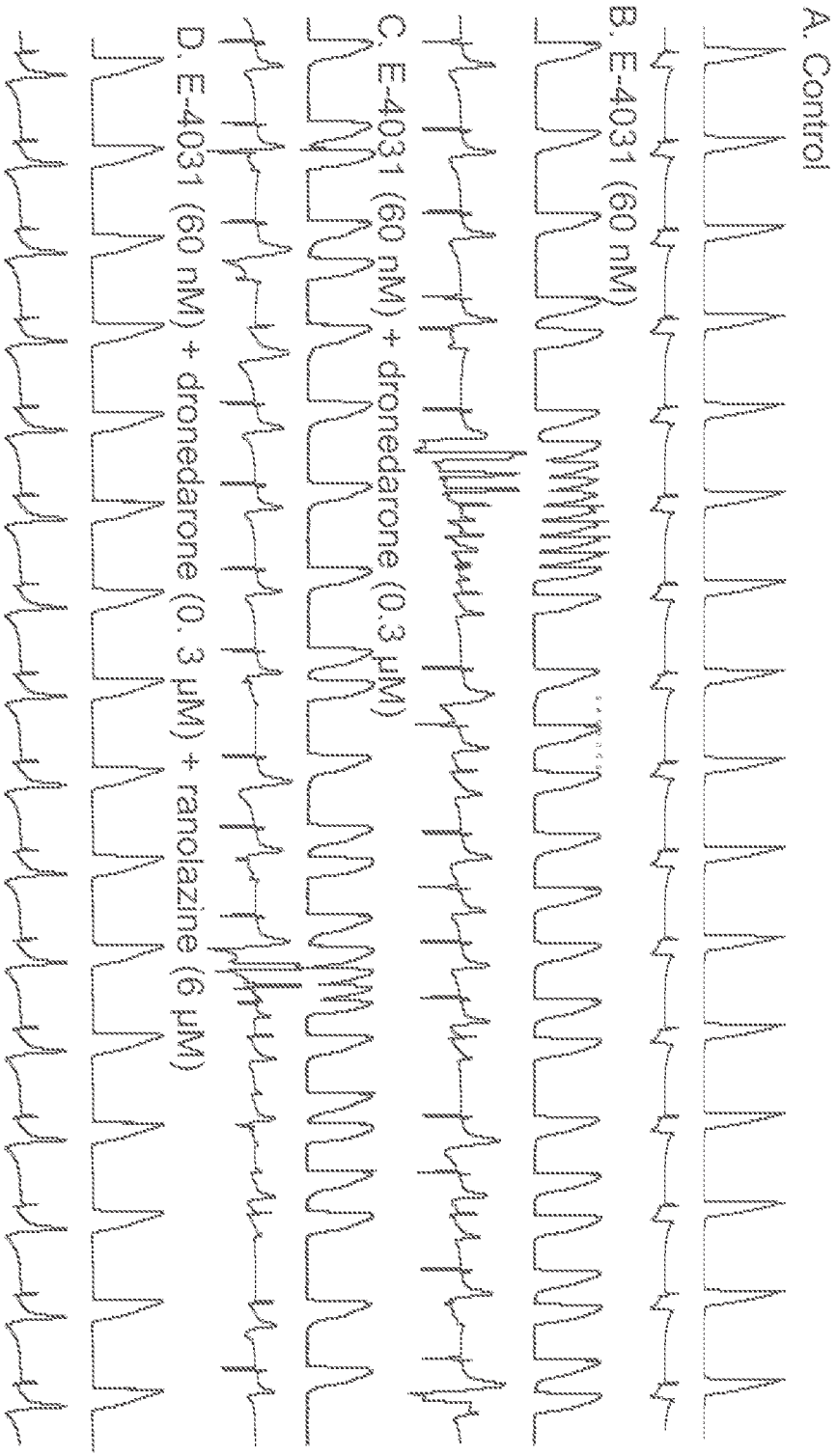

A. Control
B. E-4031 (60 nM)
C. E-4031 (60 nM) + dronedarone (0.3 uM)
D. E-4031 (60 nM) + dronedarone (0. 3 uM) + ranolazine (6 uM)

Figure 20

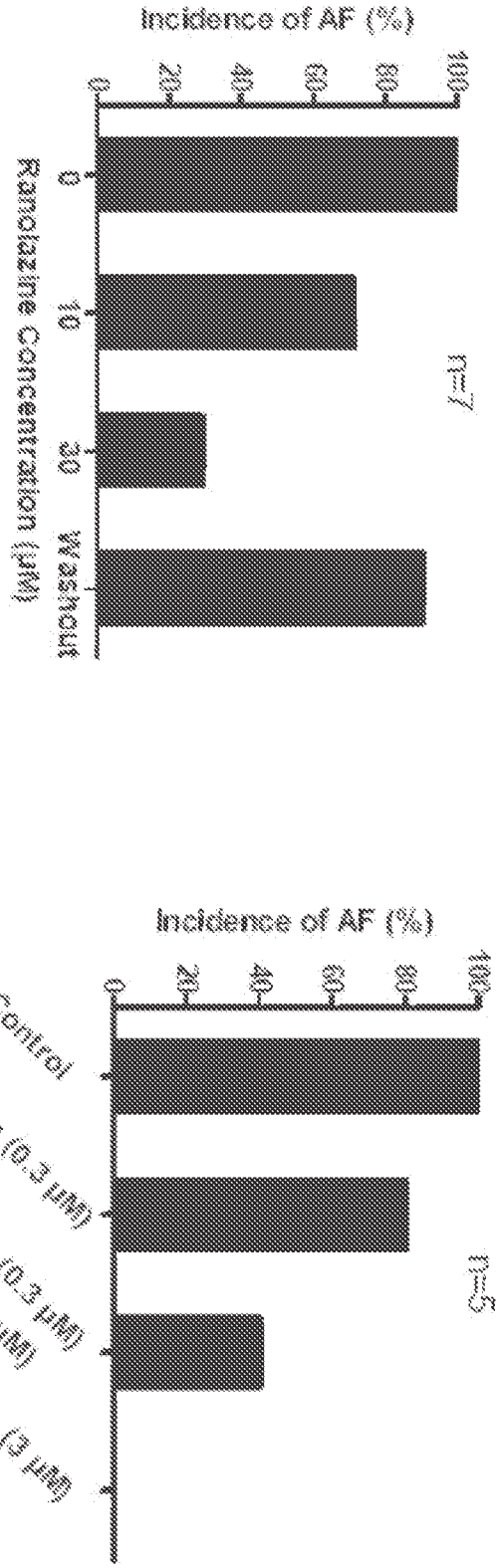

Incidence of AF (%)
0
20
40
60
80
100
Ranolazine Concentration (μM)
0
10
30
Washout
n=7
Incidence of AF (%)
0
20
40
60
80
100
Control
Dron (0.3 μM)
Dron (0.3 μM) +Ran (6 μM)
Flec (3 μM)
n=5

Figure 21

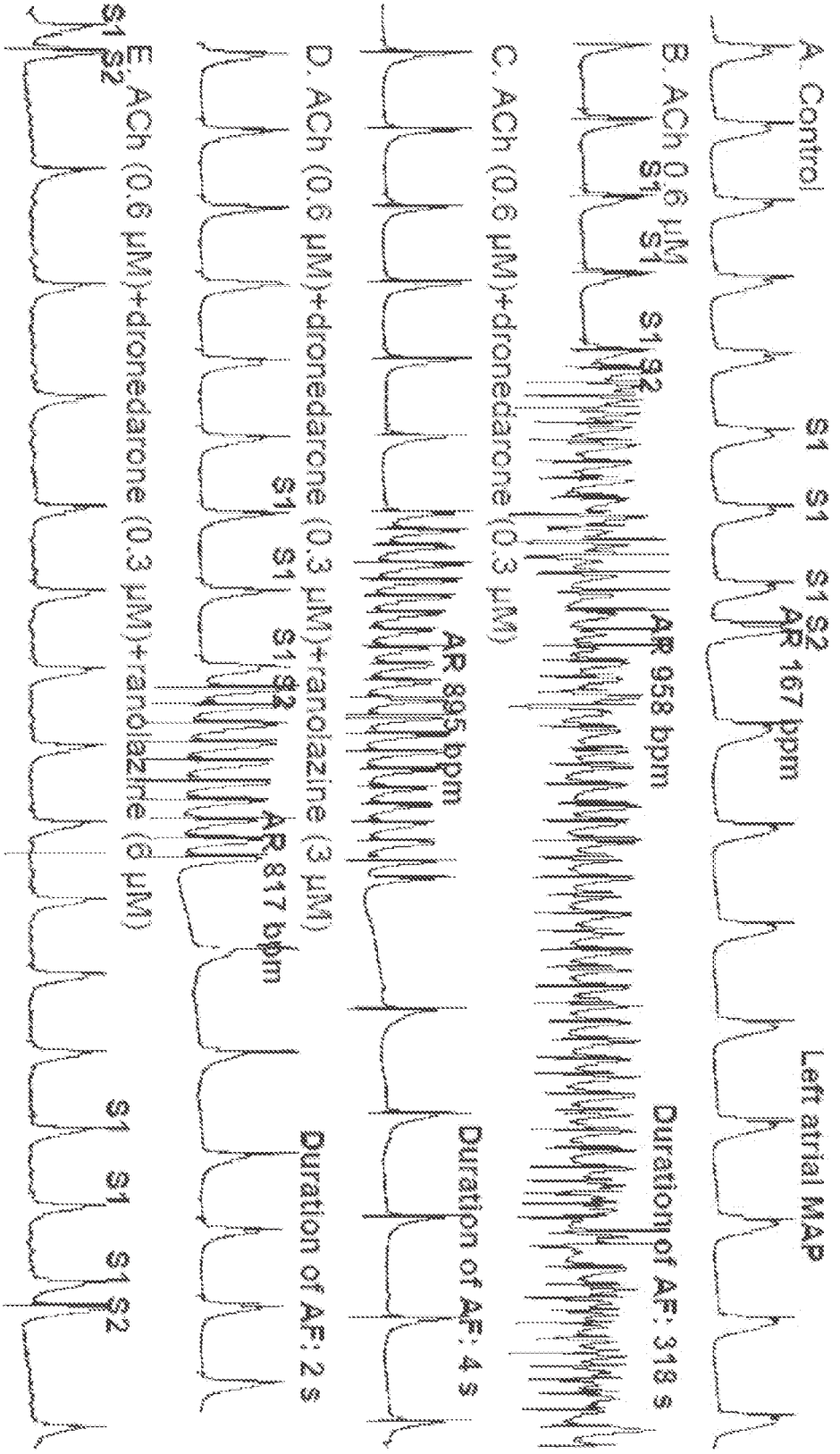

A. Control
S1 S1 S1 S2
AR 167 bpm
Left atrial MAP
B. ACh 0.6 uM
S1 S1
S1 S2
AR 958 bpm
Duration of AF: 318 s
C. ACh (0.6 uM)+dronedarone (0.3 uM)
AR 885 bpm
Duration of AF: 4 s
D. ACh (0.6 uM)+dronedarone (0.3 uM)+ranolazine (3 uM)
S1 S1 S1 S2
AR 817 bpm
Duration of AF: 2 s
E. ACh (0.6 uM)+dronedarone (0.3 uM)+ranolazine (6 uM)
S1 S2
S1 S1 S1 S2

Figure 22

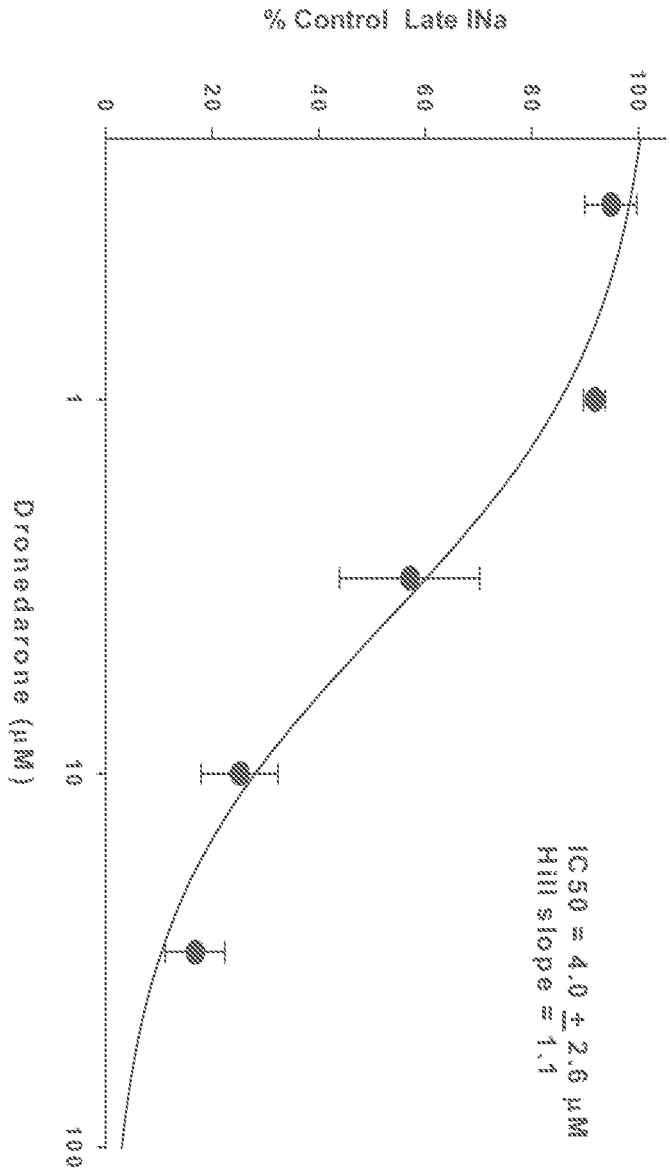

% Control Late INa
0
20
40
60
80
100
1
10
100
Dronedarone (μM)
IC50 = 4.0 +/- 2.6 μM
Hill slope = 1.1

Figure 23

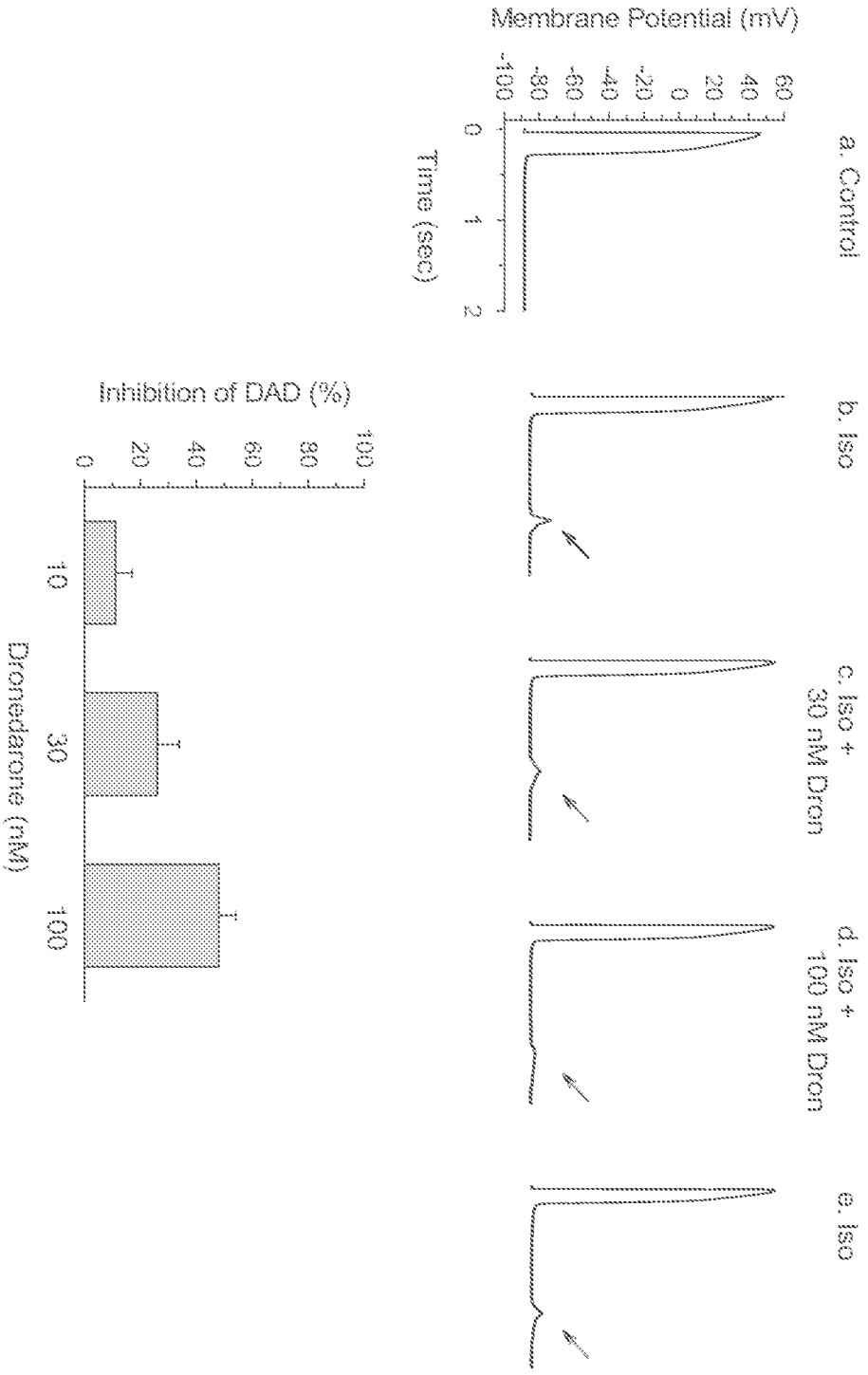

Membrane Potential (mV)
-100
-80
-60
-40
-20
0
20
40
60
Time (sec)
0
1
2
a. Control
b. Iso
c. Iso +
30 nM Dron
d. Iso +
100 nM Dron
e. Iso
Inhibition of DAD (%)
0
20
40
60
80
100
Dronedarone (nM)
10
30
100

Figure 24

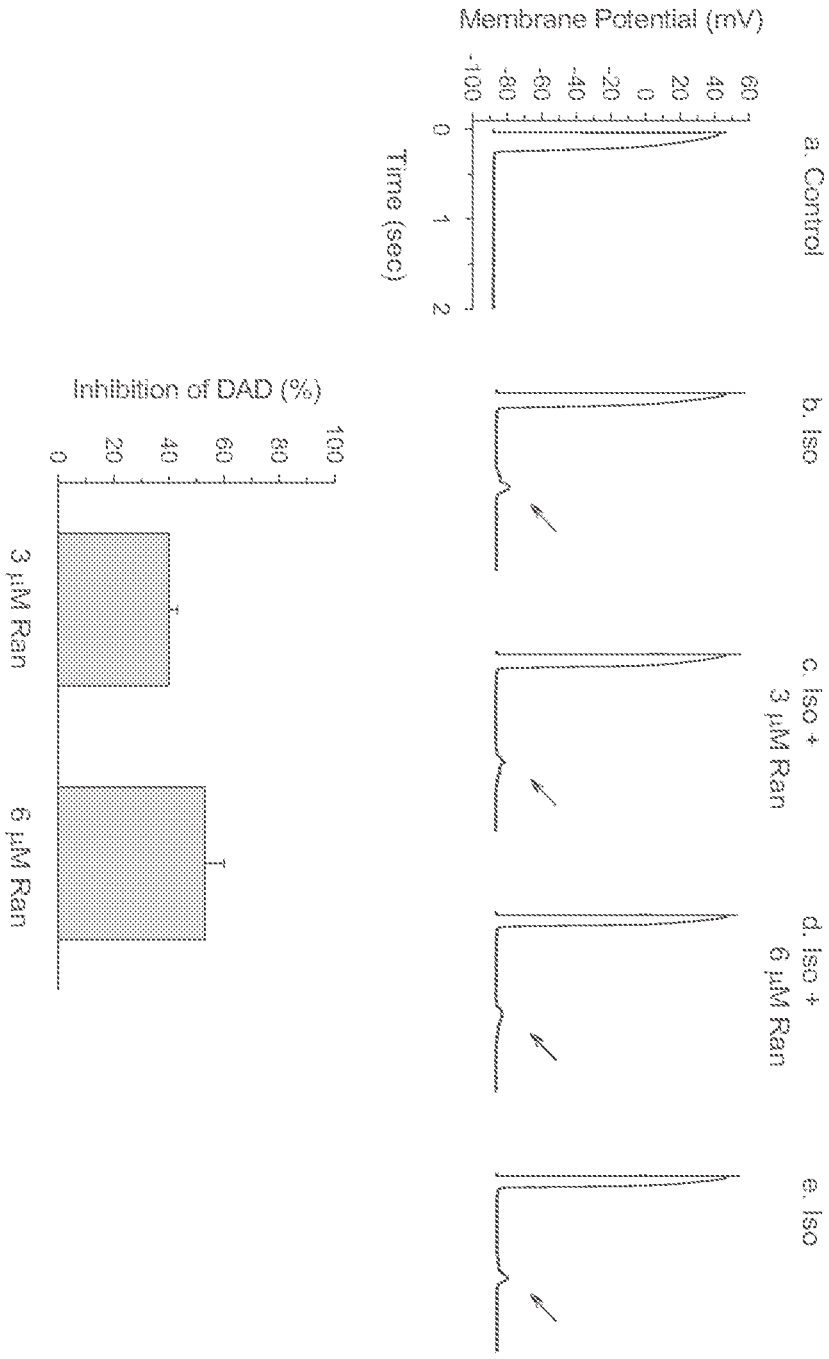

Membrane Potential (mV)
60
40
20
0
-20
-40
-60
-80
-100
0
1
2
Time (sec)
a. Control
b. Iso
c. Iso + 3 μM Ran
d. Iso + 6 μM Ran
e. Iso
Inhibition of DAD (%)
0
20
40
60
80
100
3 μM Ran
6 μM Ran

Figure 25

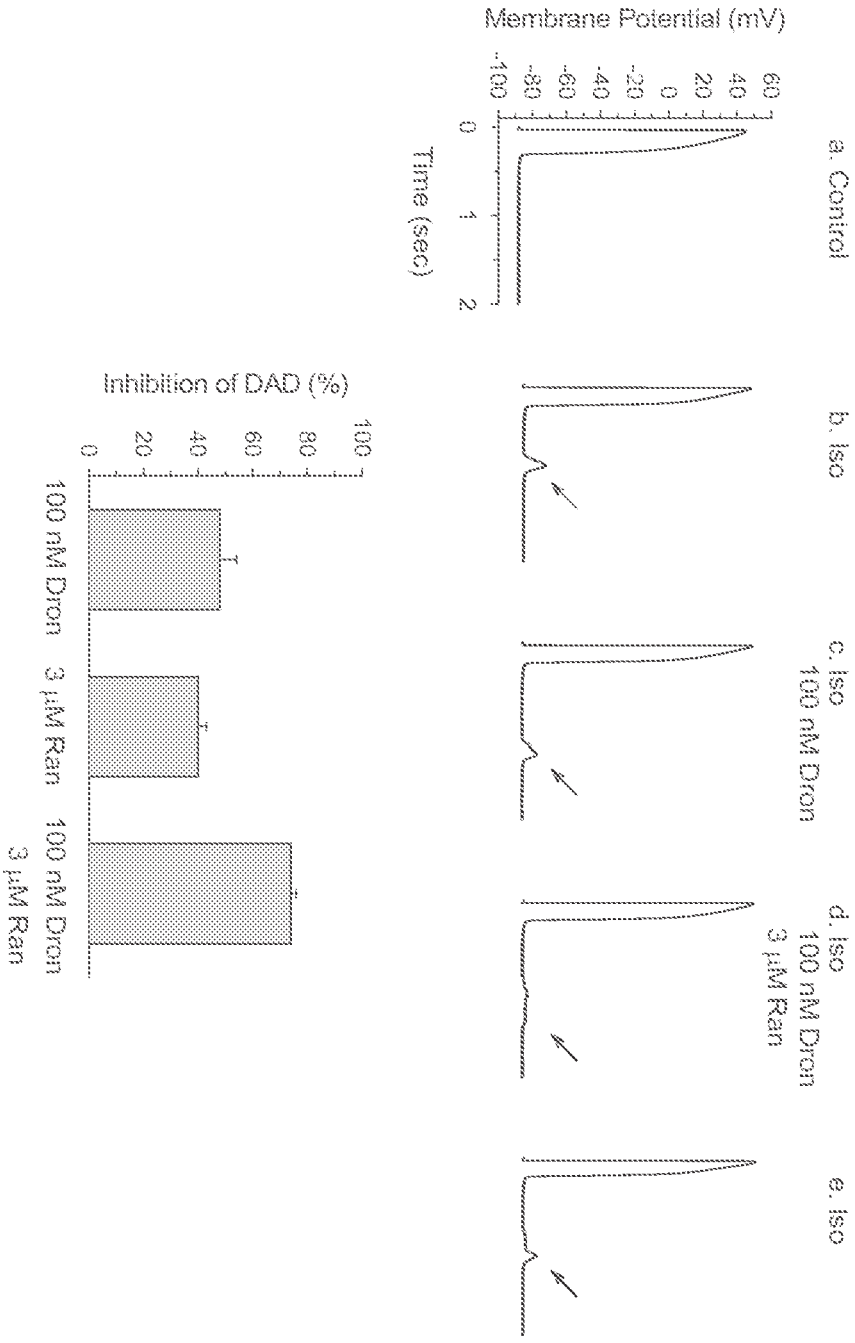

Membrane Potential (mV)
60
40
20
0
-20
-40
-60
-80
-100
0
1
2
Time (sec)
a. Control
b. Iso
c. Iso
100 nM Dron
d. Iso
100 nM Dron
3 μM Ran
e. Iso
Inhibition of DAD (%)
0
20
40
60
80
100
100 nM Dron
3 μM Ran
100 nM Dron
3 μM Ran

Figure 26