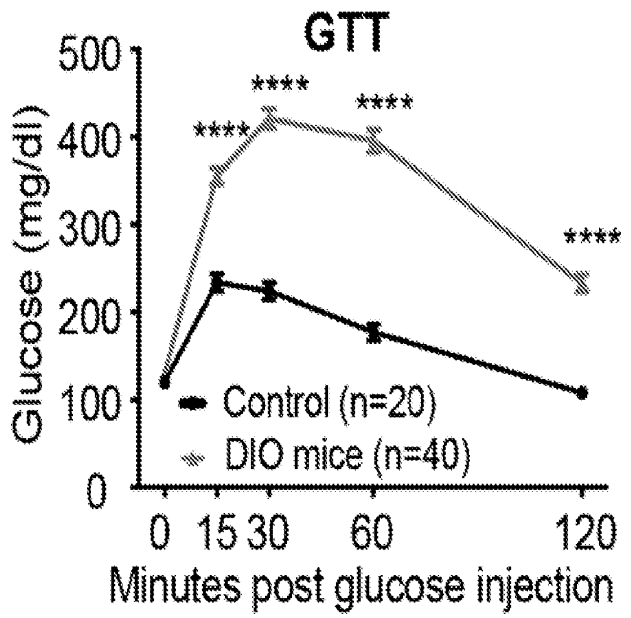

GTT
Glucose (mg/dl)
500
400
300
200
100
0
****
****
****
****
Control (n=20)
DIO mice (n=40)
0 15 30 60 120
Minutes post glucose injection

FIG. 1A

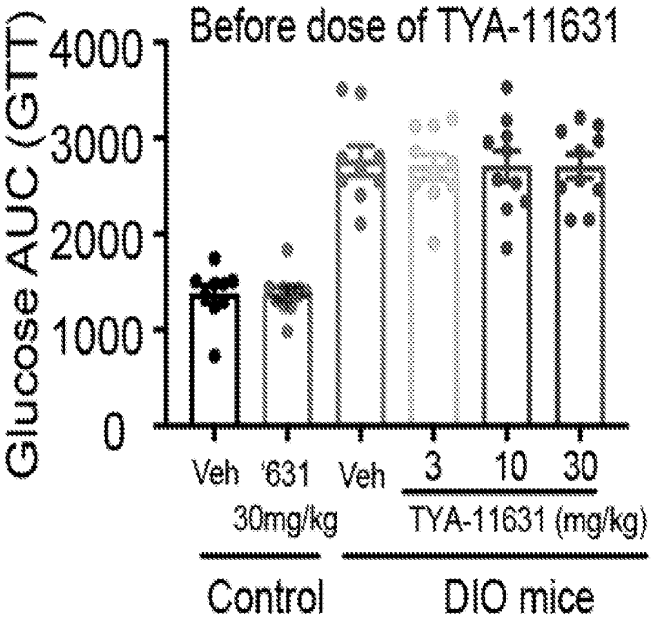

Before dose of TYA-11631
Glucose AUC (GTT)
4000
3000
2000
1000
0
Veh
'631
30mg/kg
Veh
3
10
30
TYA-11631 (mg/kg)
Control
DIO mice

FIG. 1B

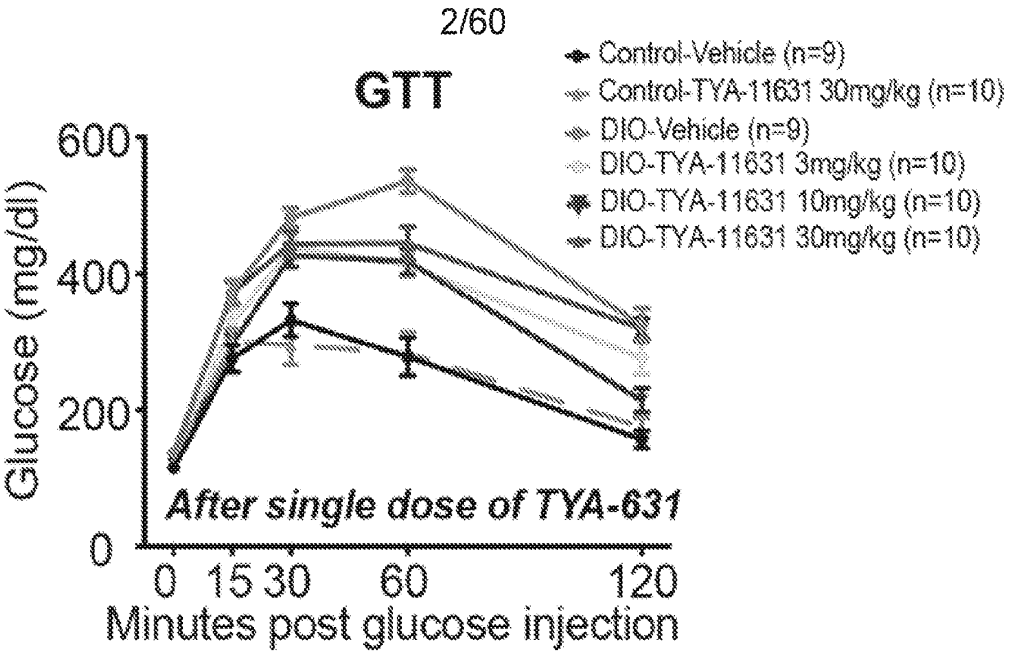

GTT
Control-Vehicle (n=9)
Control-TYA-11631 30mg/kg (n=10)
DIO-Vehicle (n=9)
DIO-TYA-11631 3mg/kg (n=10)
DIO-TYA-11631 10mg/kg (n=10)
DIO-TYA-11631 30mg/kg (n=10)
Glucose (mg/dl)
600
400
200
0
After single dose of TYA-631
0 15 30 60 120
Minutes post glucose injection

FIG. 1C

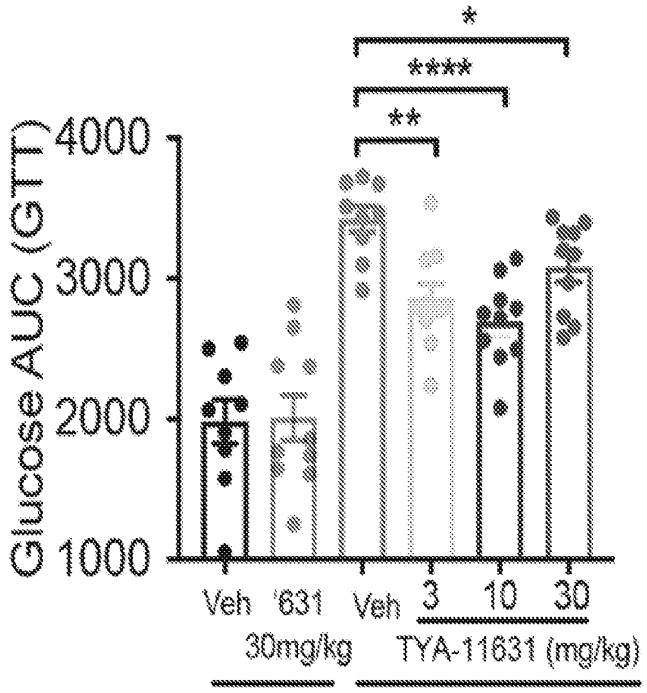

*
****
**
Glucose AUC (GTT)
4000
3000
2000
1000
Veh '631 Veh 3 10 30
30mg/kg TYA-11631 (mg/kg)

FIG. 1D

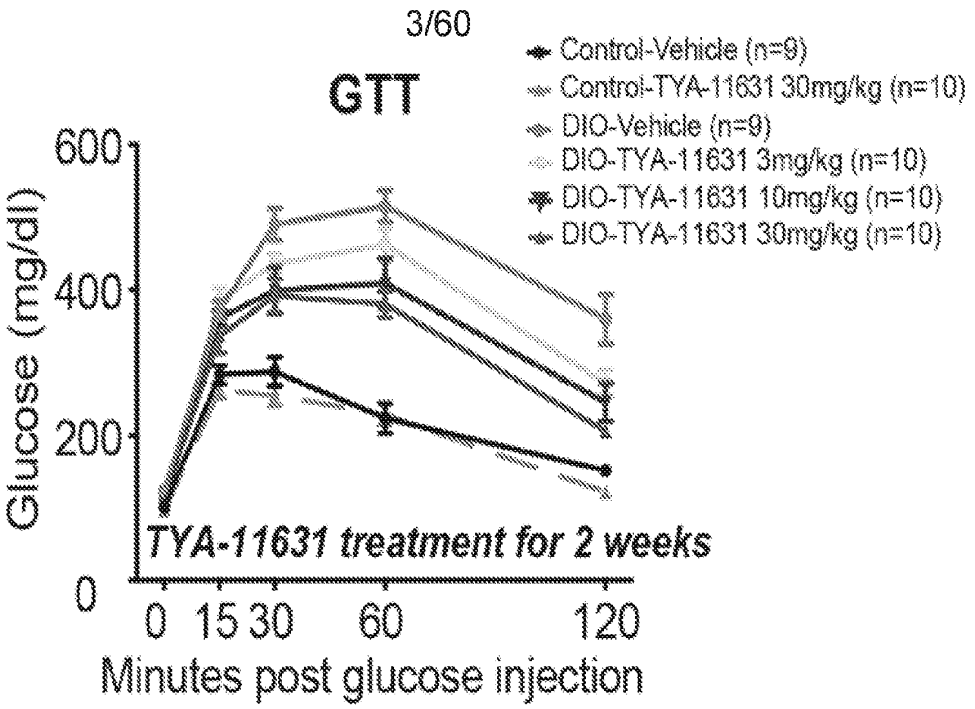

GTT
Control-Vehicle (n=9)
Control-TYA-11631 30mg/kg (n=10)
DIO-Vehicle (n=9)
DIO-TYA-11631 3mg/kg (n=10)
DIO-TYA-11631 10mg/kg (n=10)
DIO-TYA-11631 30mg/kg (n=10)
Glucose (mg/dl)
600
400
200
0
TYA-11631 treatment for 2 weeks
0 15 30 60 120
Minutes post glucose injection

FIG. 1E

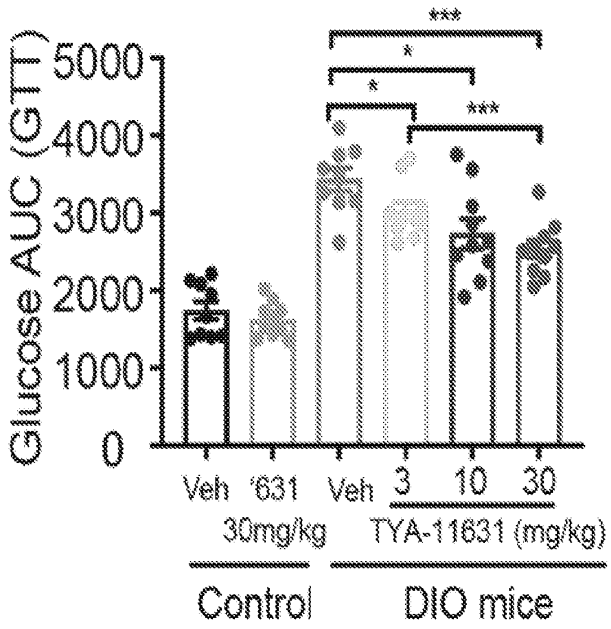

Glucose AUC (GTT)
5000
4000
3000
2000
1000
0
***
*
*
***
Veh
'631
30mg/kg
Veh
3
10
30
TYA-11631 (mg/kg)
Control
DIO mice

FIG. 1F

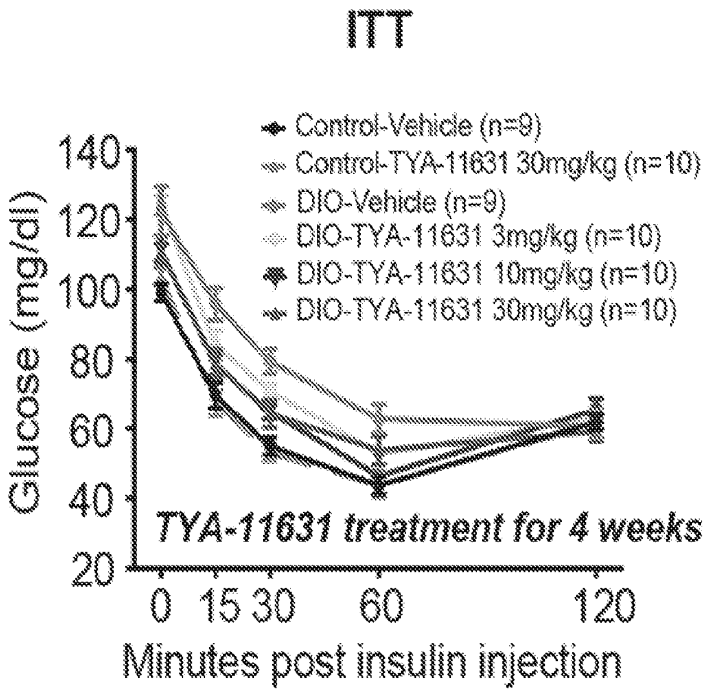

ITT
Control-Vehicle (n=9)
Control-TYA-11631 30mg/kg (n=10)
DIO-Vehicle (n=9)
DIO-TYA-11631 3mg/kg (n=10)
DIO-TYA-11631 10mg/kg (n=10)
DIO-TYA-11631 30mg/kg (n=10)
Glucose (mg/dl)
140
120
100
80
60
40
20
TYA-11631 treatment for 4 weeks
0 15 30 60 120
Minutes post insulin injection

FIG. 1G

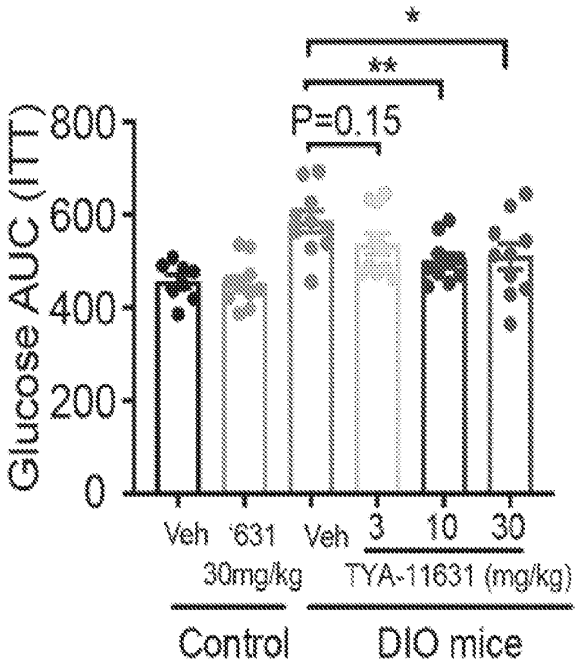

*
**
P=0.15
Glucose AUC (ITT)
800
600
400
200
0
Veh 631 Veh 3 10 30
30mg/kg TYA-11631 (mg/kg)
Control DIO mice

FIG. 1H

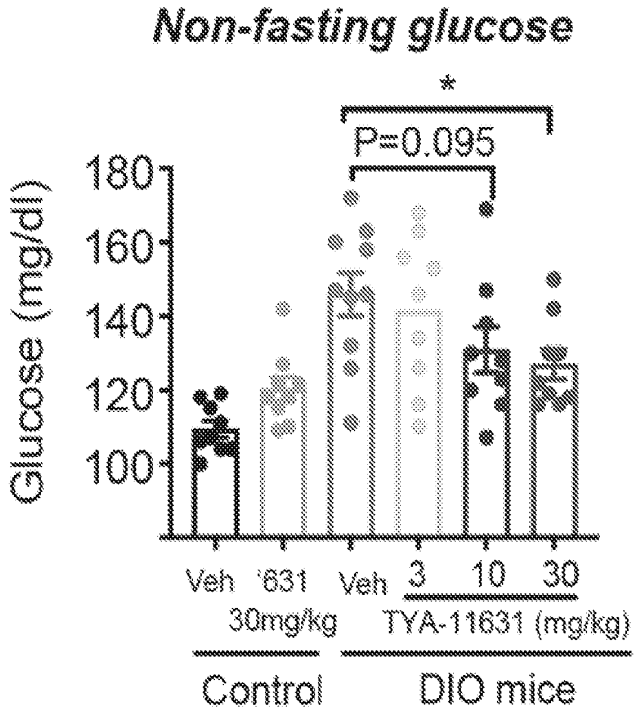

Non-fasting glucose
*
P=0.095
Glucose (mg/dl)
180
160
140
120
100
Veh
'631
30mg/kg
Veh
3
10
30
TYA-11631 (mg/kg)
Control
DIO mice

FIG. 1I

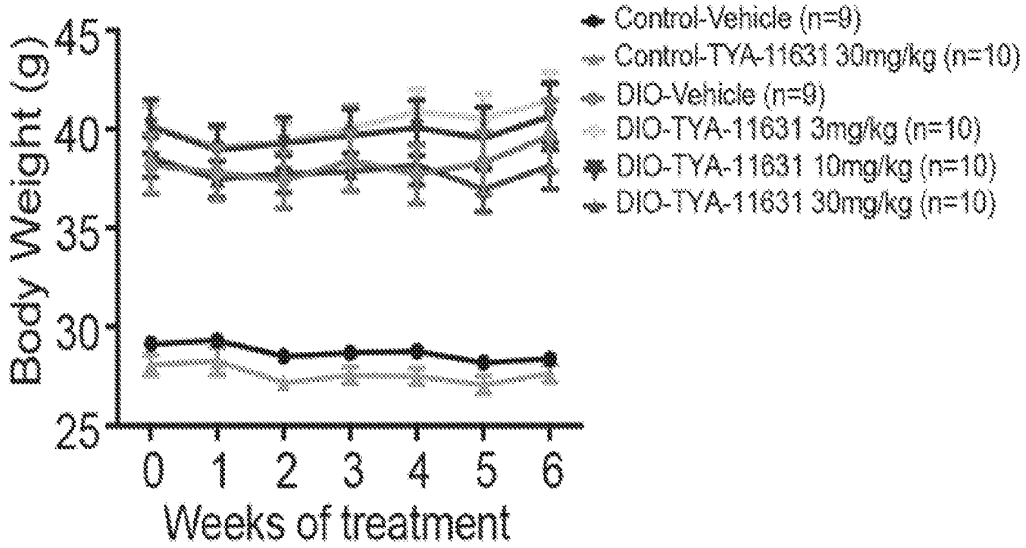

Body Weight (g)
45
40
35
30
25
0
1
2
3
4
5
6
Weeks of treatment
Control-Vehicle (n=9)
Control-TYA-11631 30mg/kg (n=10)
DIO-Vehicle (n=9)
DIO-TYA-11631 3mg/kg (n=10)
DIO-TYA-11631 10mg/kg (n=10)
DIO-TYA-11631 30mg/kg (n=10)

FIG. 1J

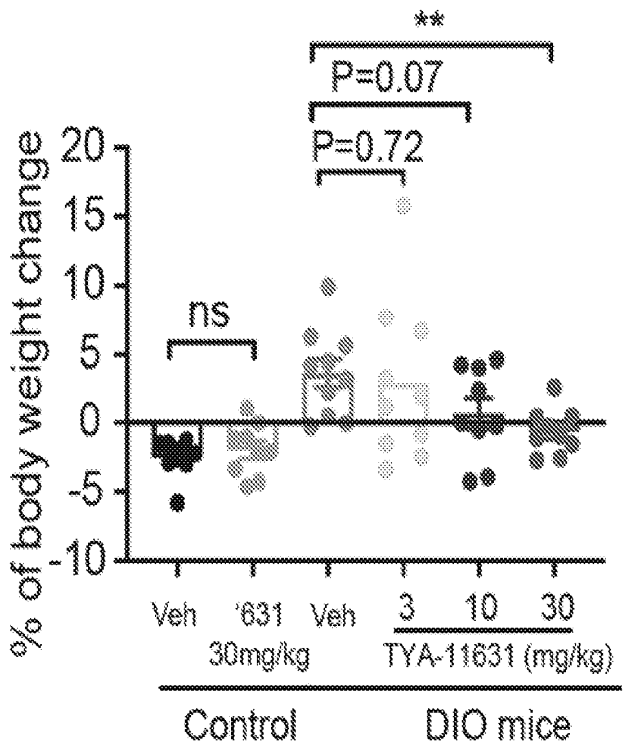

**
P=0.07
P=0.72
ns
% of body weight change
20
15
10
5
0
-5
-10
Veh
'631
30mg/kg
Veh
3
10
30
TYA-11631 (mg/kg)
Control
DIO mice

FIG. 1K

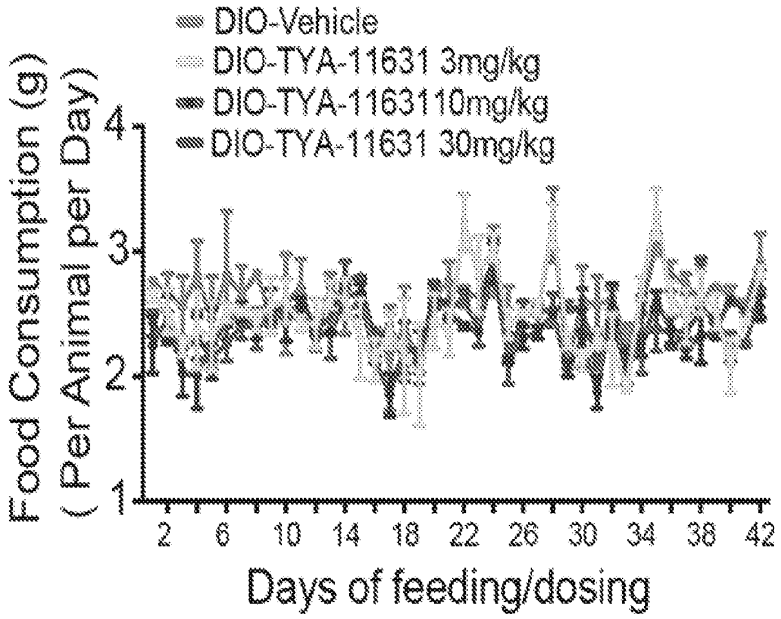

DIO-Vehicle
DIO-TYA-11631 3mg/kg
DIO-TYA-1163110mg/kg
DIO-TYA-11631 30mg/kg
Food Consumption (g)
(Per Animal per Day)
4
3
2
1
2
6
10
14
18
22
26
30
34
38
42
Days of feeding/dosing

FIG. 1L

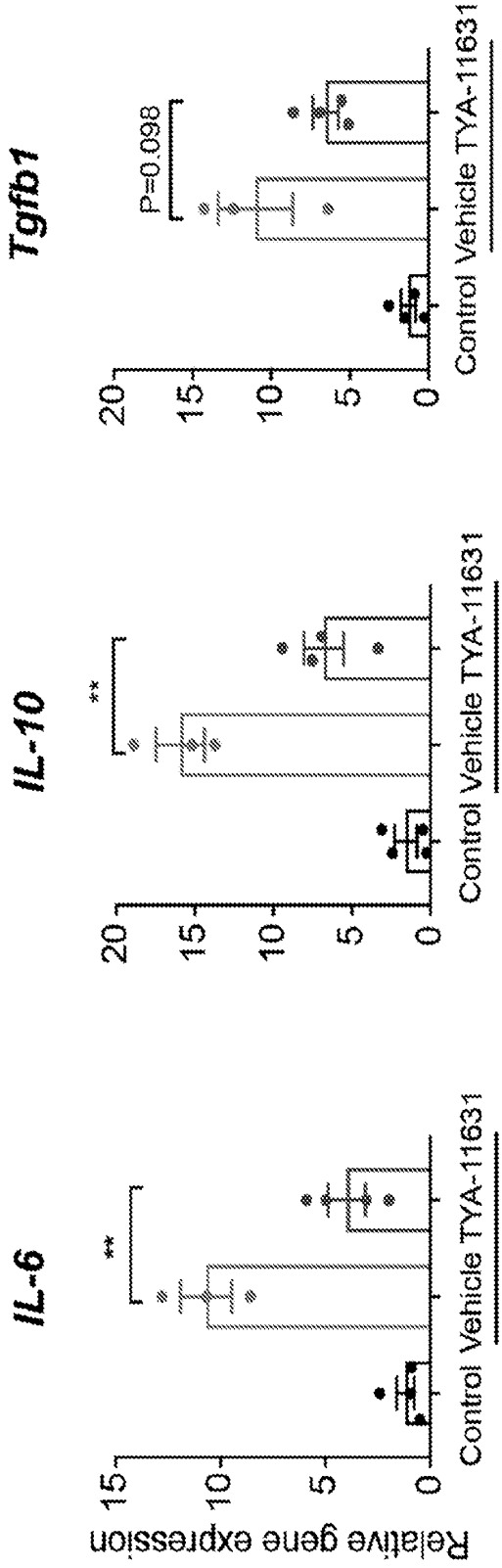


FIG. 2A

FIG. 2B

FIG. 2C

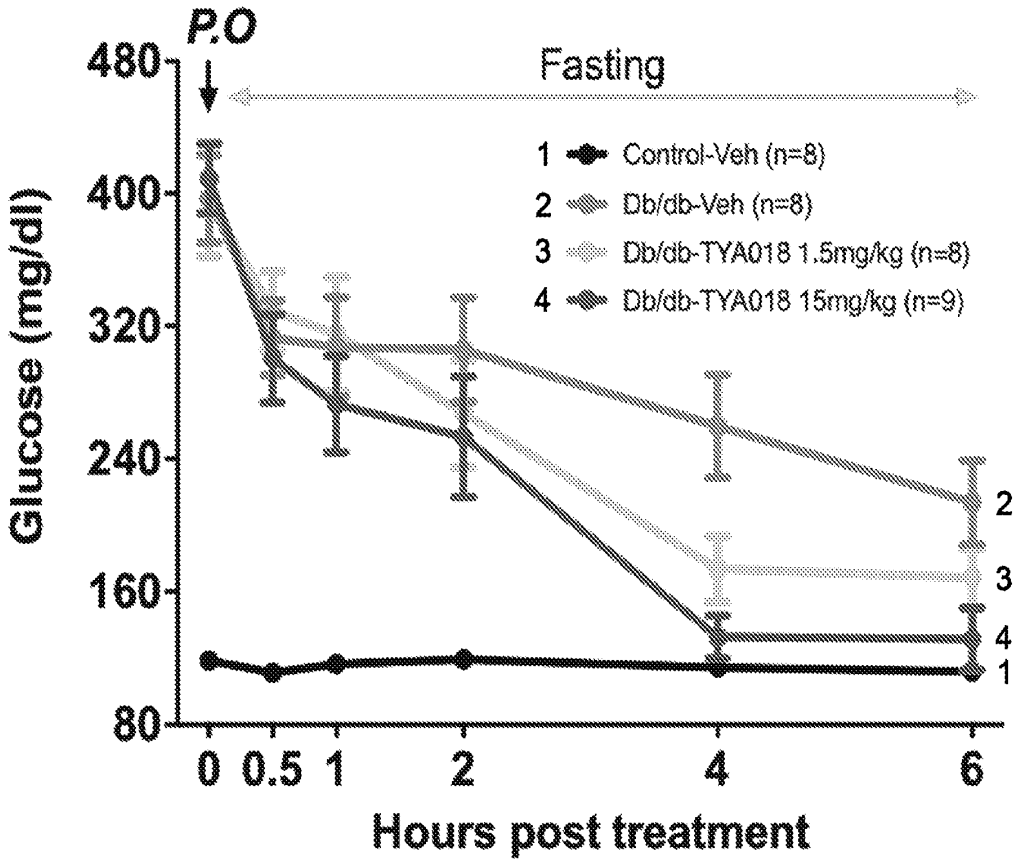

P.O
Fasting
480
400
320
240
160
80
Glucose (mg/dl)
1 Control-Veh (n=8)
2 Db/db-Veh (n=8)
3 Db/db-TYA018 1.5mg/kg (n=8)
4 Db/db-TYA018 15mg/kg (n=9)
0 0.5 1 2 4 6
Hours post treatment

FIG. 3A

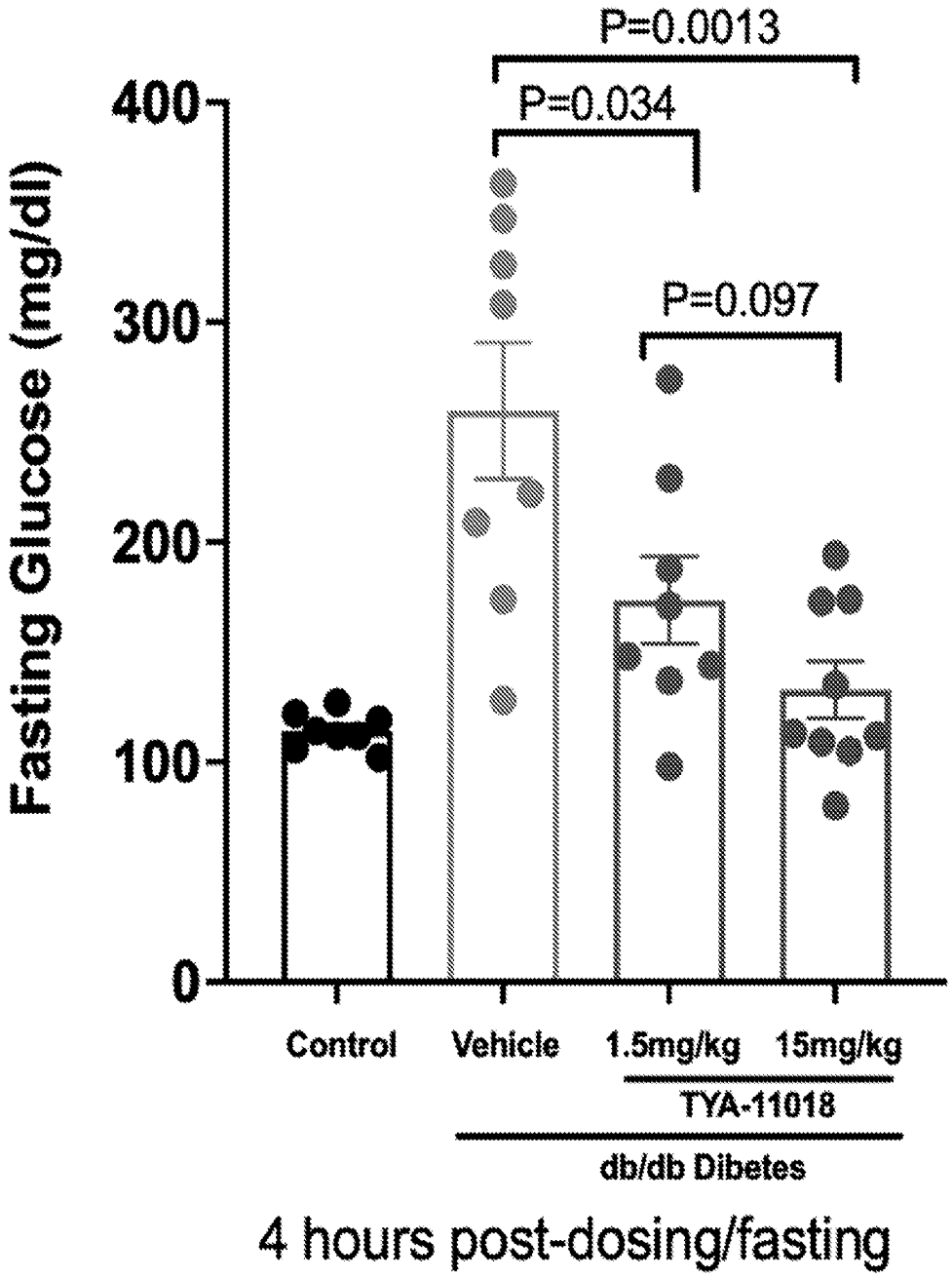

P=0.0013
P=0.034
P=0.097
Fasting Glucose (mg/dl)
400
300
200
100
0
Control
Vehicle
1.5mg/kg
15mg/kg
TYA-11018
db/db Dibetes
4 hours post-dosing/fasting

FIG. 3B

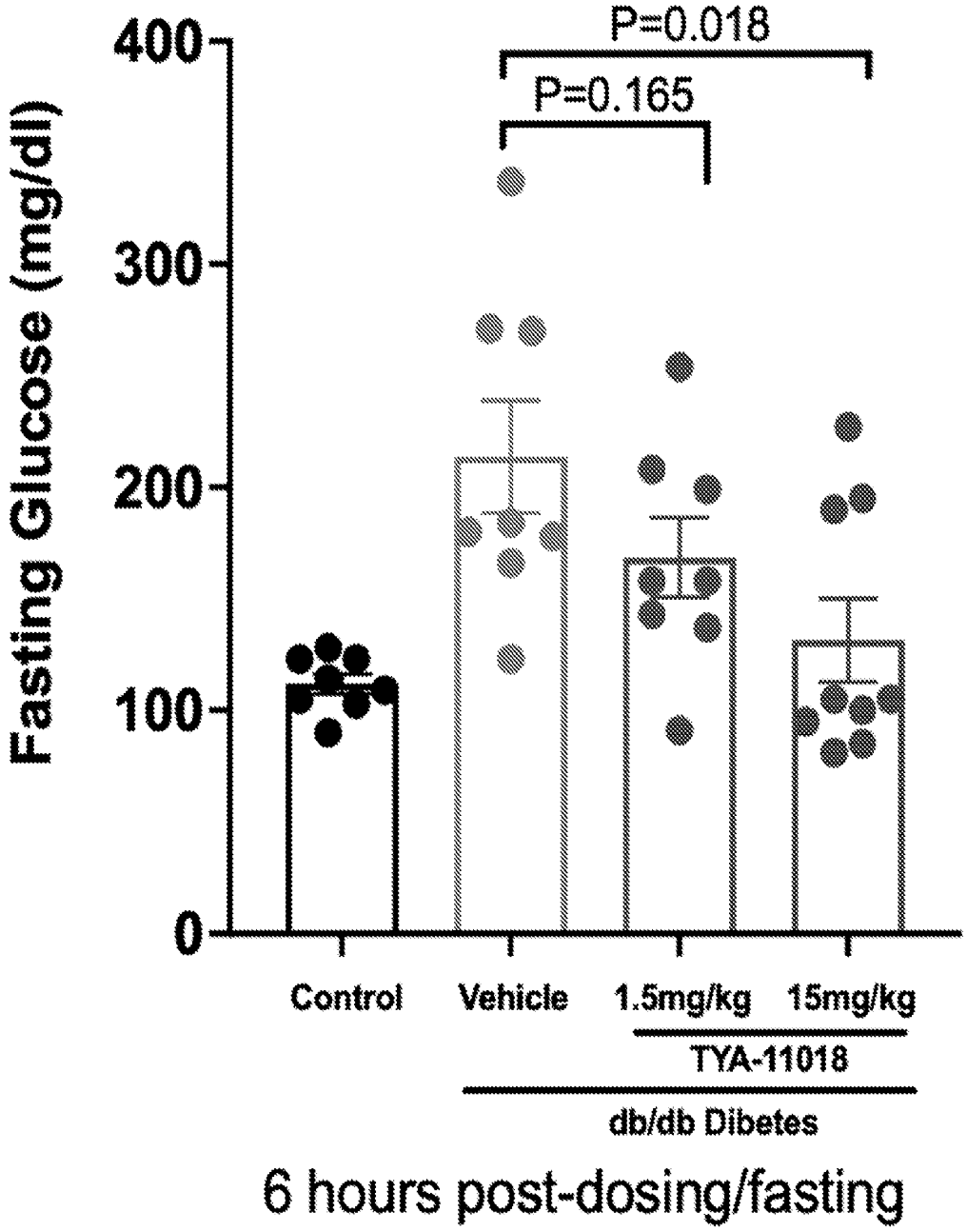

P=0.018
P=0.165
400
300
200
100
0
Fasting Glucose (mg/dl)
Control
Vehicle
1.5mg/kg
15mg/kg
TYA-11018
db/db Dibetes
6 hours post-dosing/fasting

FIG. 3C

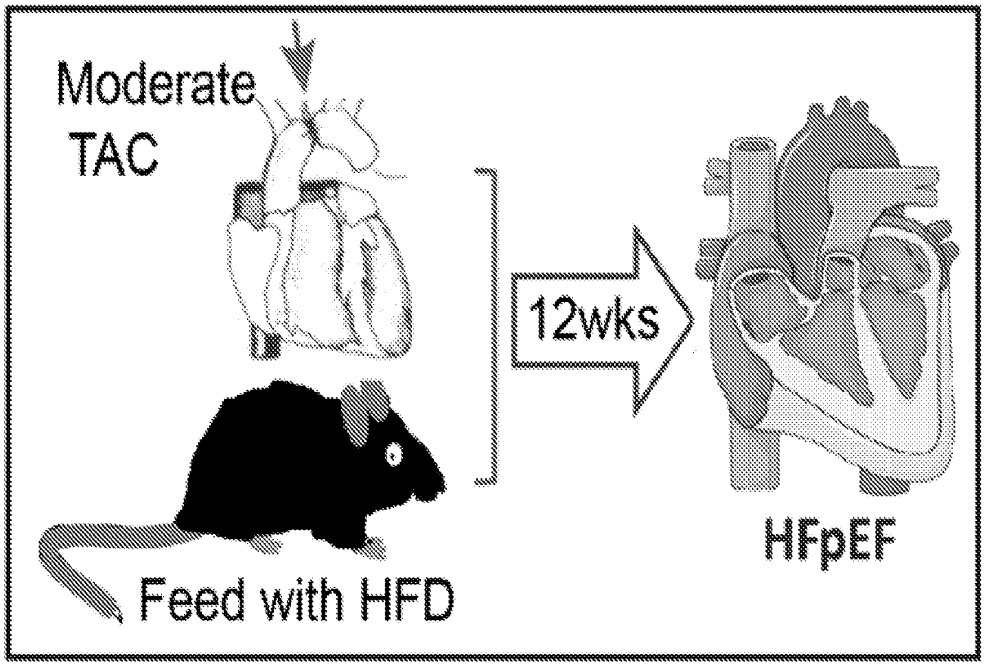


FIG. 4A

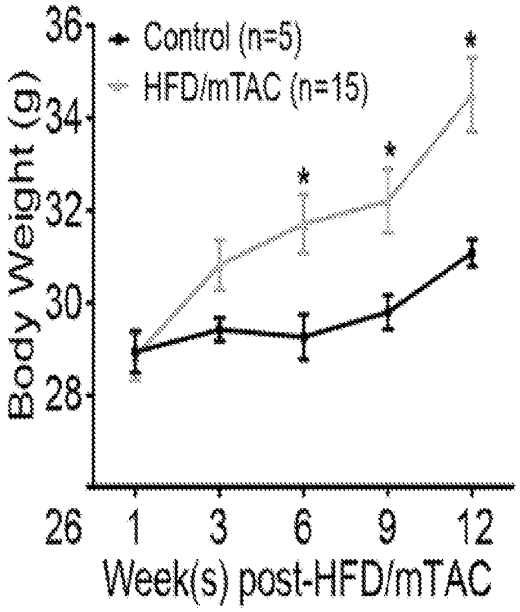

Control (n=5)
HFD/mTAC (n=15)
Body Weight (g)
36
34
32
30
28
26
1
3
6
9
12
Week(s) post-HFD/mTAC
*
*
*

FIG. 4B

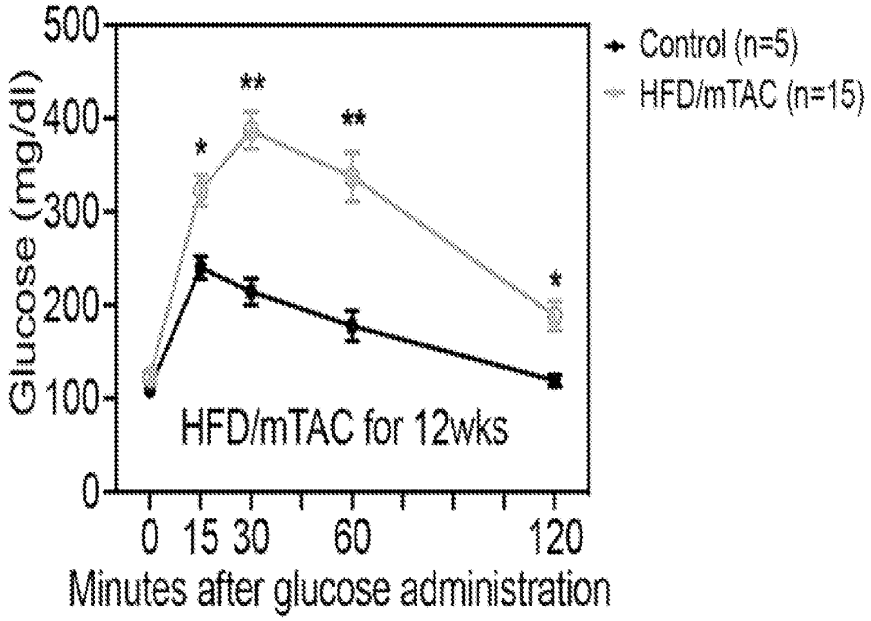

Control (n=5)
HFD/mTAC (n=15)
Glucose (mg/dl)
500
400
300
200
100
0
HFD/mTAC for 12wks
0
15
30
60
120
Minutes after glucose administration
*
**
**
*

FIG. 4C

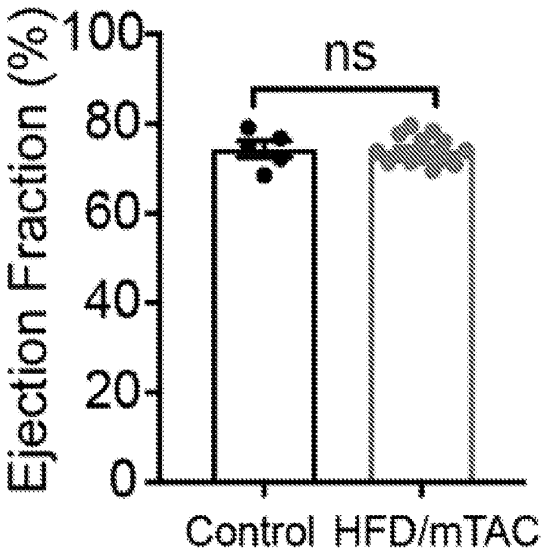

Ejection Fraction (%)
100
80
60
40
20
0
ns
Control
HFD/mTAC

FIG. 4D

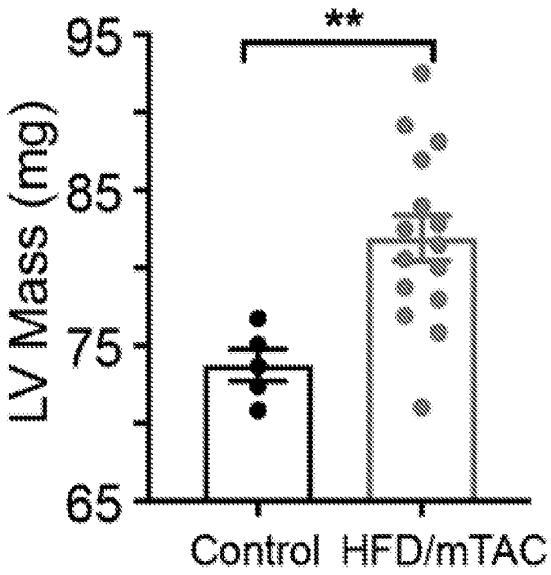

LV Mass (mg)
95
85
75
65
**
Control
HFD/mTAC

FIG. 4E

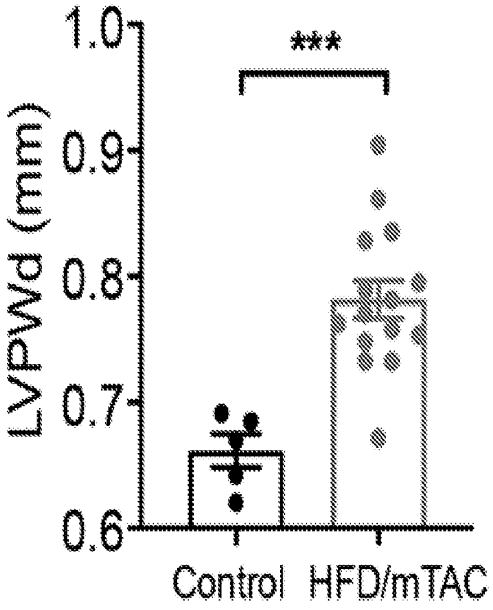

1.0
0.9
0.8
0.7
0.6
LVPWd (mm)
***
Control
HFD/mTAC

FIG. 4F

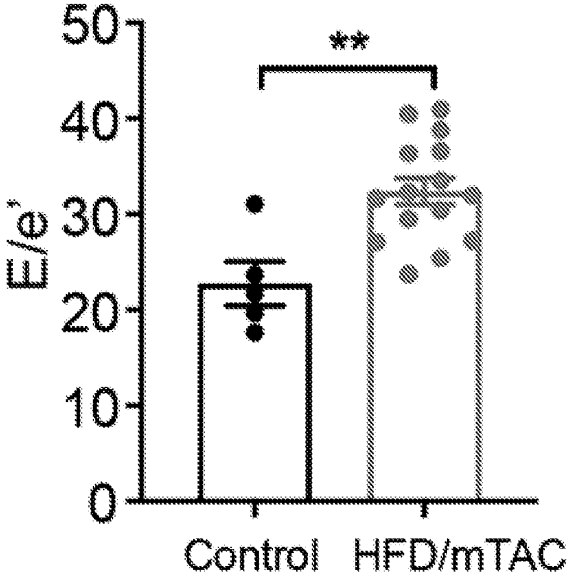

50
40
30
20
10
0
E/e'
**
Control
HFD/mTAC

FIG. 4G

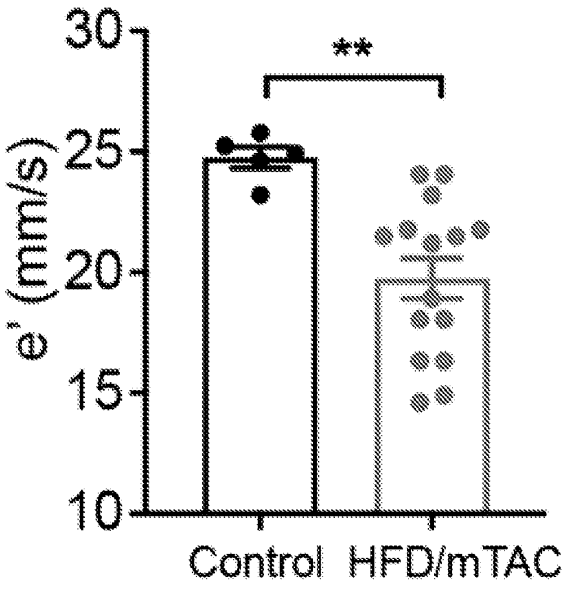


FIG. 4H

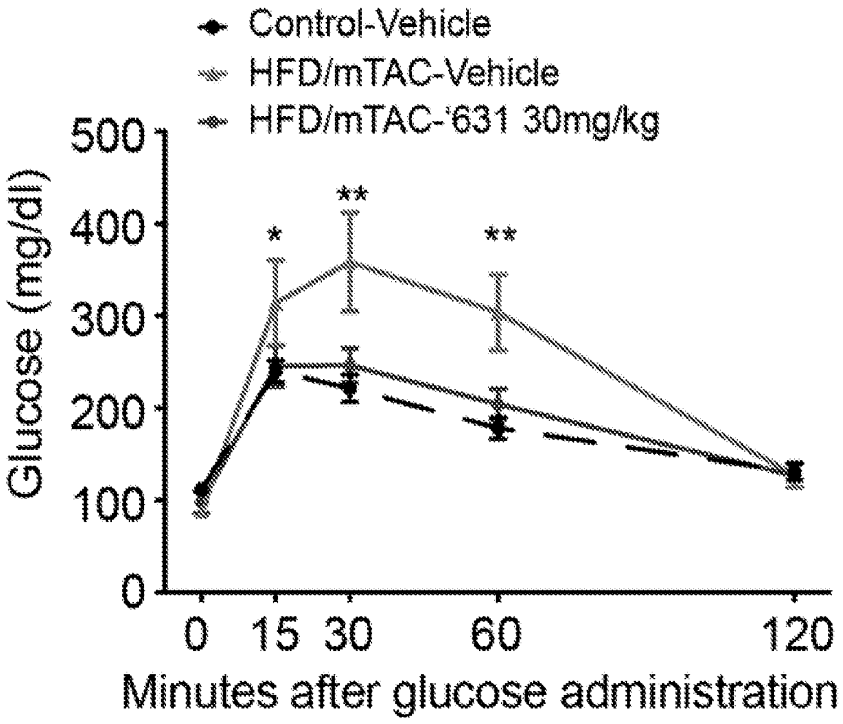

Control-Vehicle
HFD/mTAC-Vehicle
HFD/mTAC-'631 30mg/kg
Glucose (mg/dl)
500
400
300
200
100
0
*
**
**
0
15
30
60
120
Minutes after glucose administration

FIG. 5A

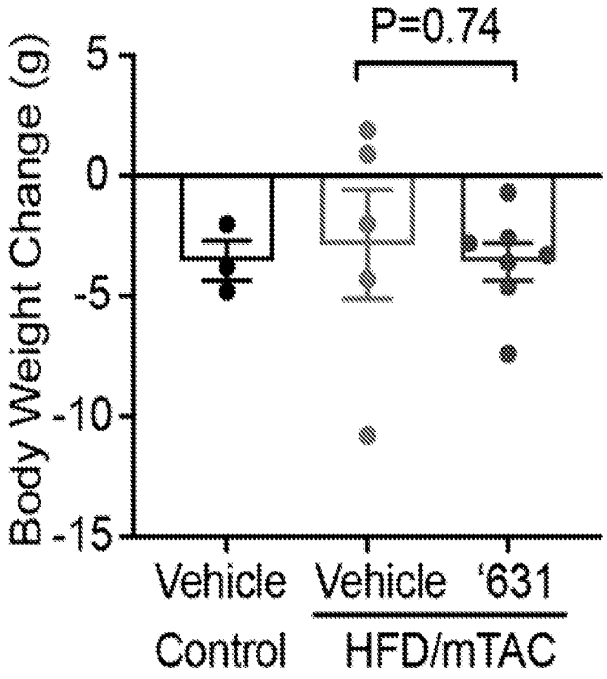

P=0.74
Body Weight Change (g)
5
0
-5
-10
-15
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 5B

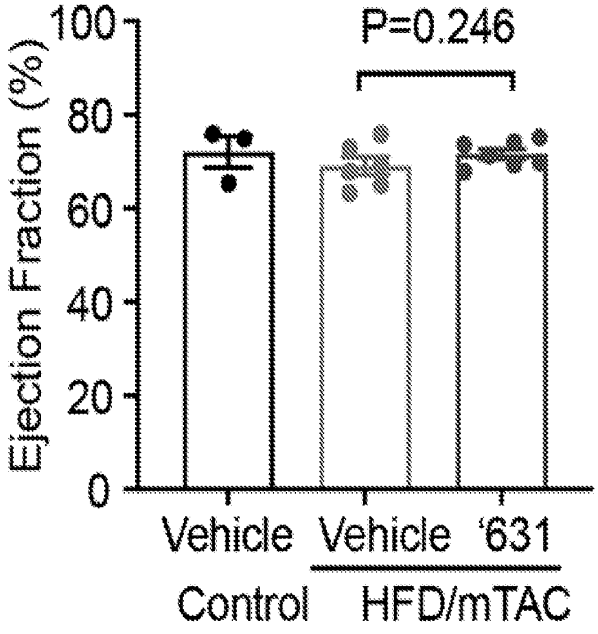

P=0.246
Ejection Fraction (%)
100
80
60
40
20
0
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 5C

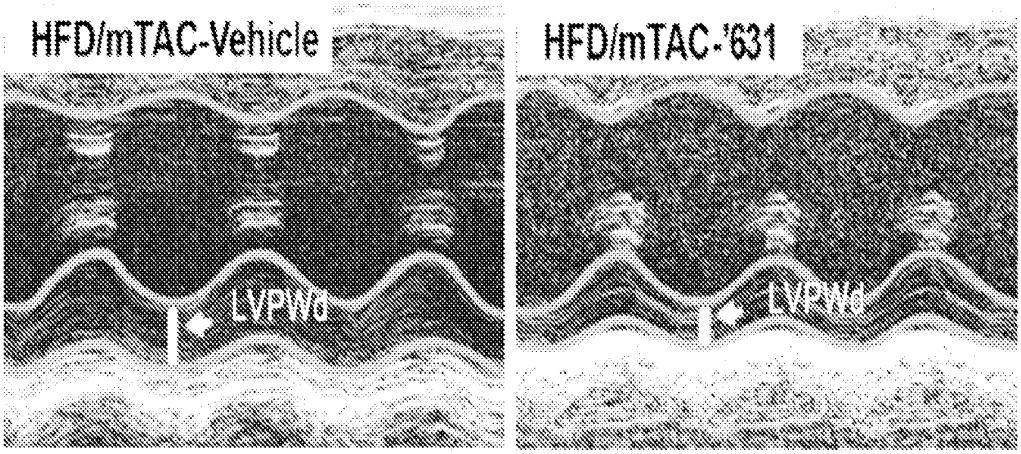


FIG. 5D

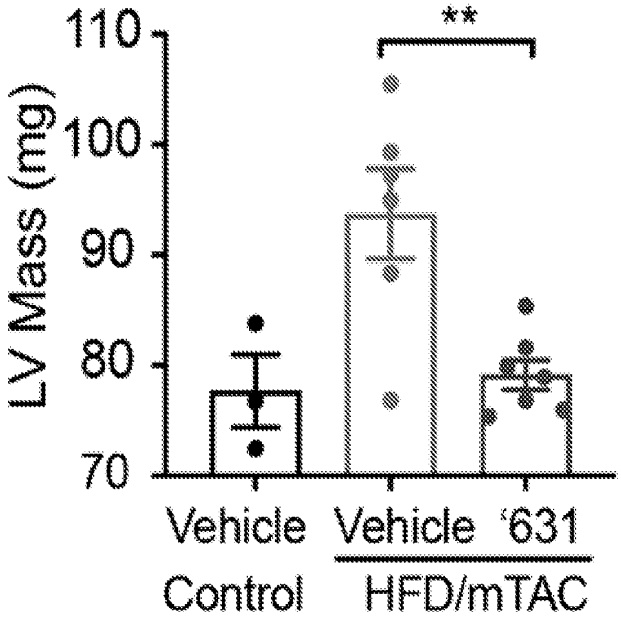

**
110
100
90
80
70
LV Mass (mg)
Vehicle
Vehicle '631
Control
HFD/mTAC

FIG. 5E

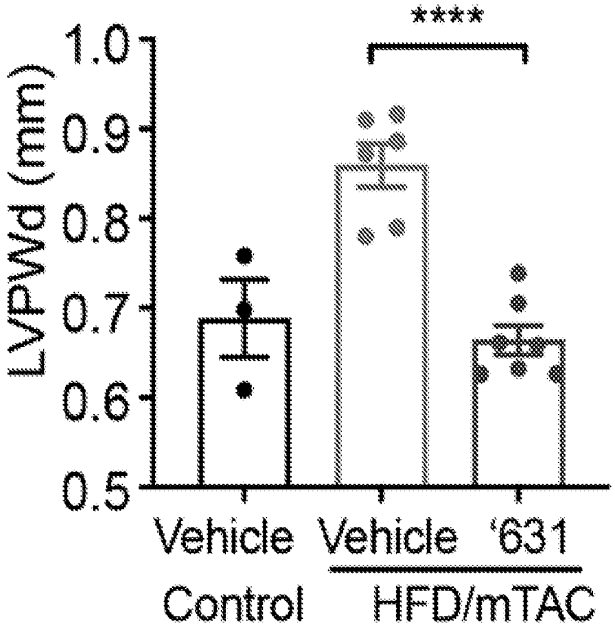

****
1.0
0.9
0.8
0.7
0.6
0.5
LVPWd (mm)
Vehicle
Vehicle '631
Control
HFD/mTAC

FIG. 5F

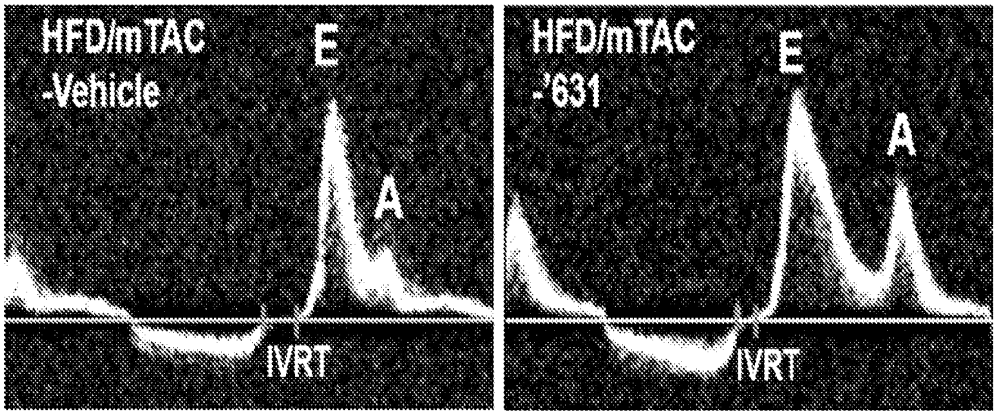


FIG. 5G

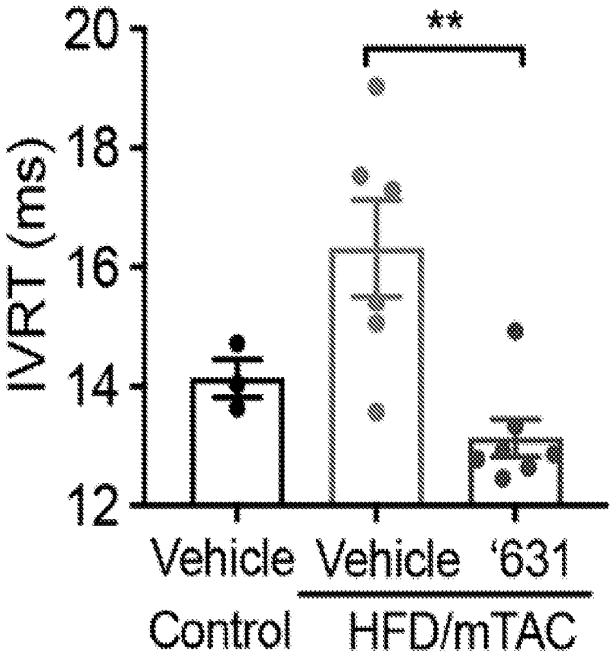

**
IVRT (ms)
20
18
16
14
12
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 5H

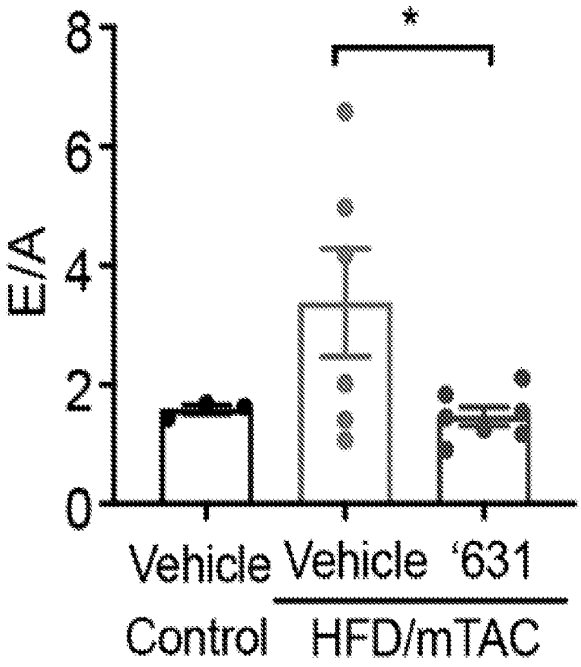

*
E/A
8
6
4
2
0
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 5I

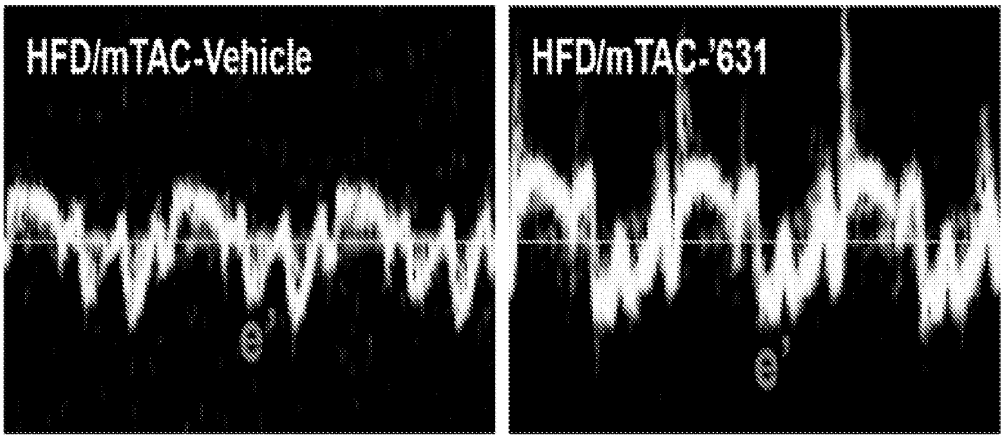


FIG. 5J

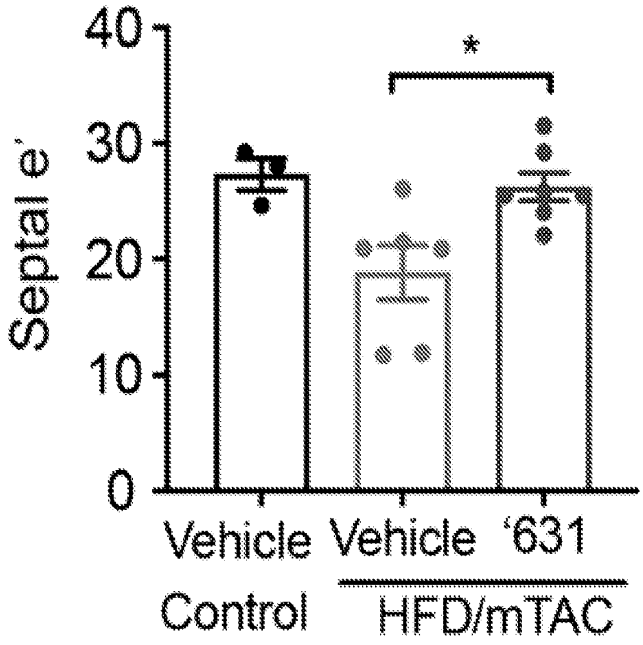

Septal e'
40
30
20
10
0
*
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 5K

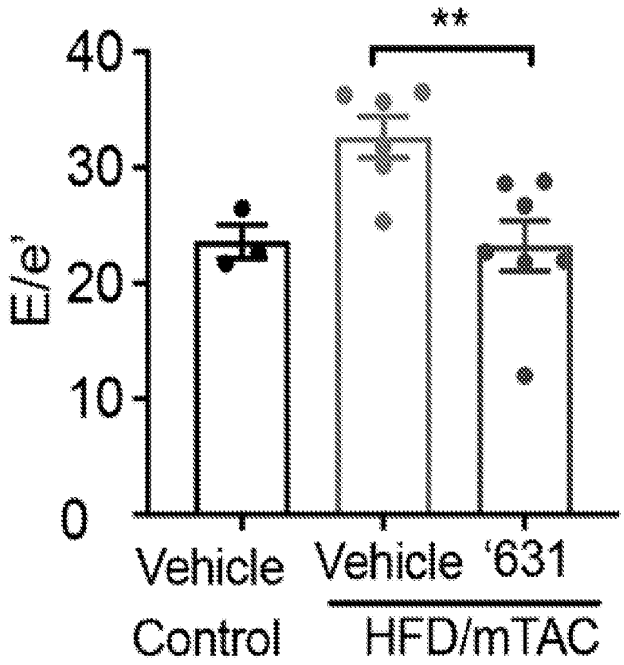

E/e'
40
30
20
10
0
**
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 5L

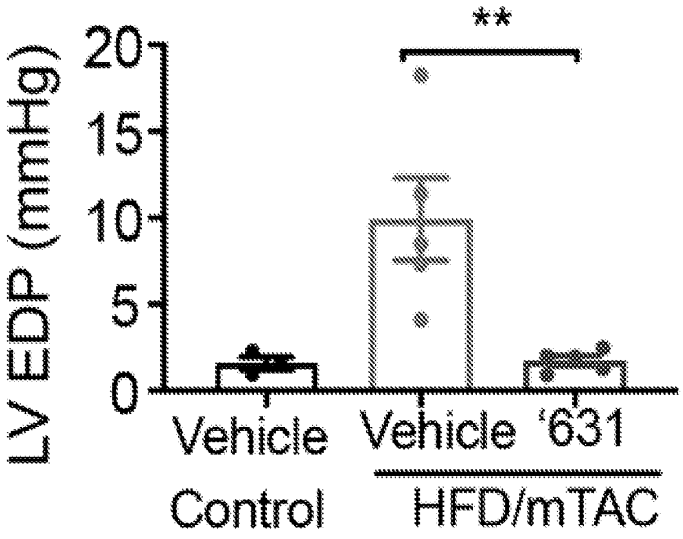


FIG. 5M

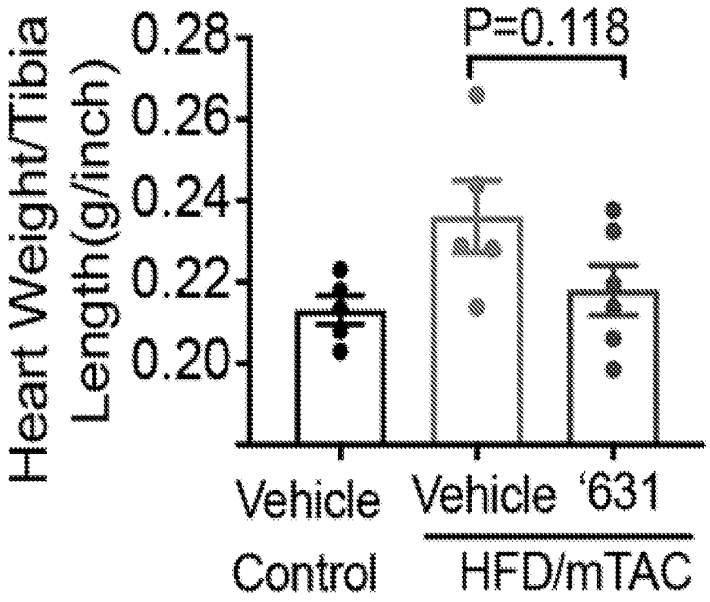

Heart Weight/Tibia Length(g/inch)
0.28
0.26
0.24
0.22
0.20
P=0.118
Vehicle
Control
Vehicle '631
HFD/mTAC

FIG. 5N

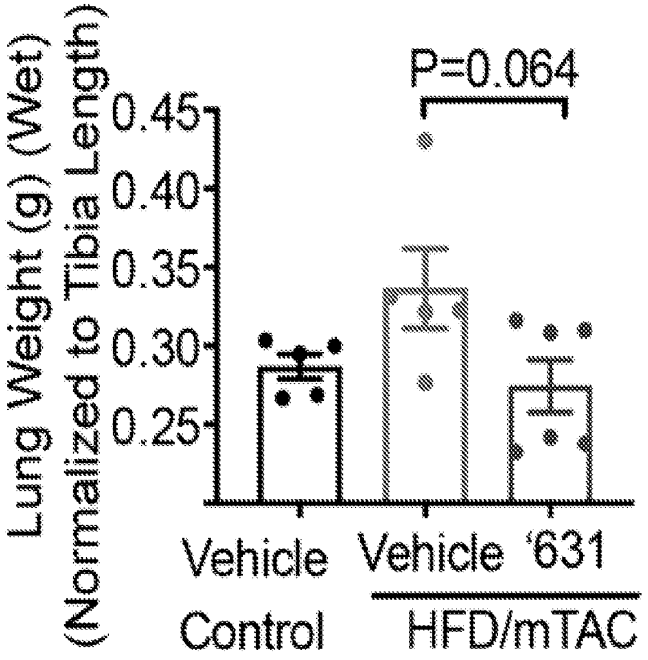

Lung Weight (g) (Wet) (Normalized to Tibia Length)
0.45
0.40
0.35
0.30
0.25
P=0.064
Vehicle
Control
Vehicle '631
HFD/mTAC

FIG. 5O

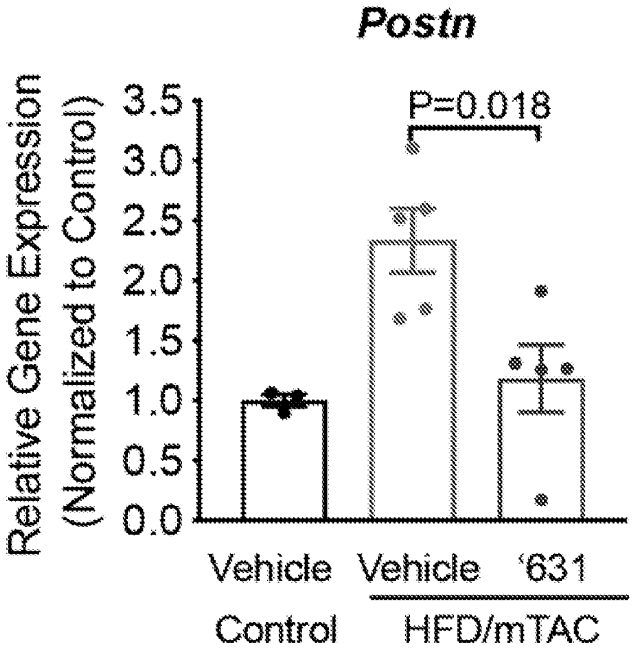

Postn
Relative Gene Expression
(Normalized to Control)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
P=0.018
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 6A

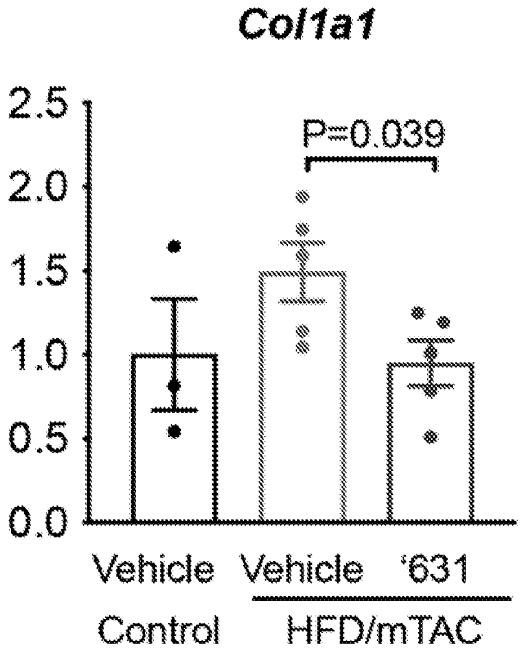

Col1a1
2.5
2.0
1.5
1.0
0.5
0.0
P=0.039
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 6B

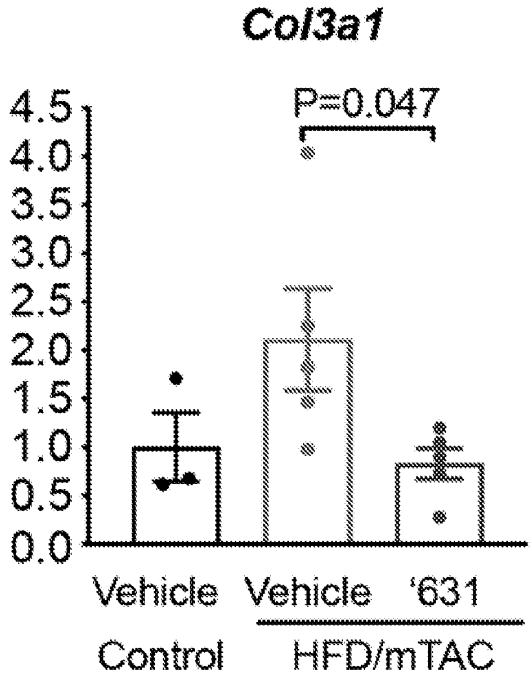

Col3a1
P=0.047
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 6C

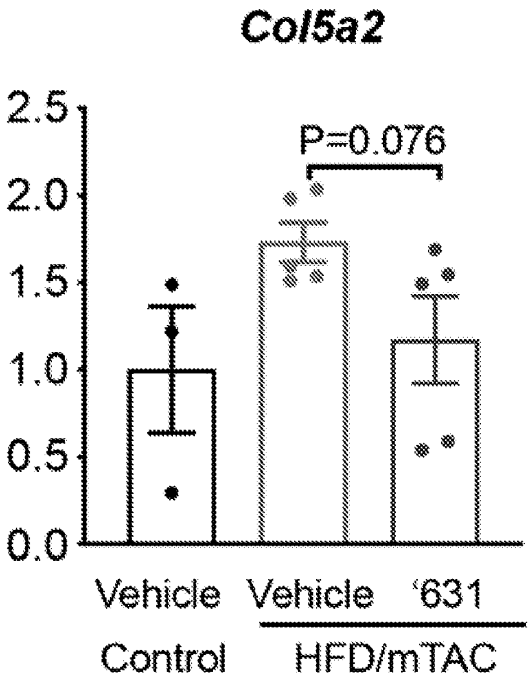

Col5a2
P=0.076
2.5
2.0
1.5
1.0
0.5
0.0
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 6D

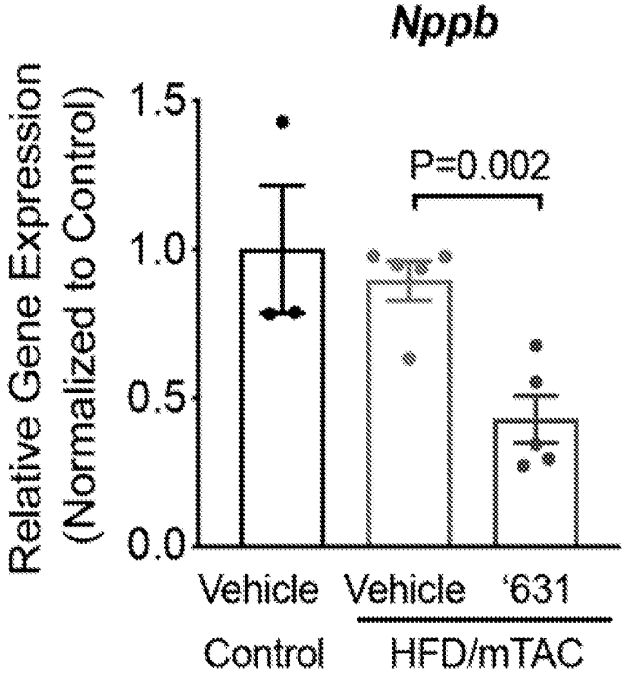

Nppb
Relative Gene Expression
(Normalized to Control)
1.5
1.0
0.5
0.0
P=0.002
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 6E

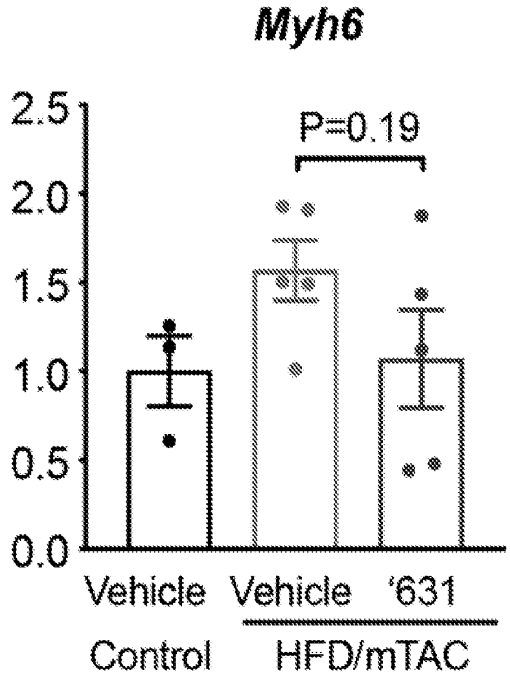

Myh6
2.5
2.0
1.5
1.0
0.5
0.0
P=0.19
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 6F

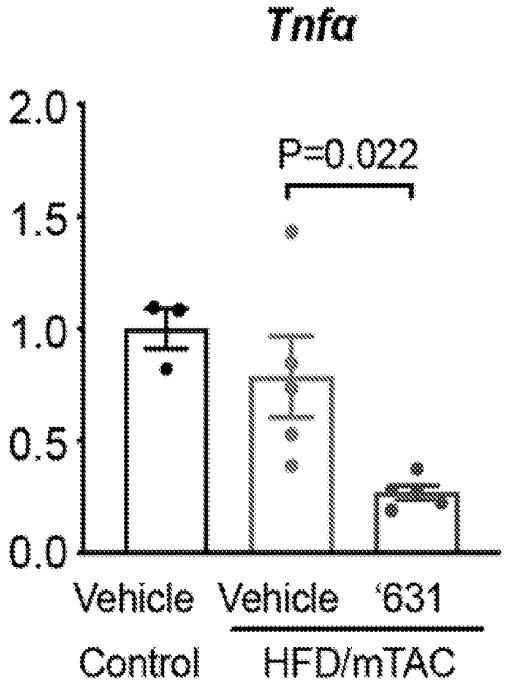

Tnfα
2.0
1.5
1.0
0.5
0.0
P=0.022
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 6G

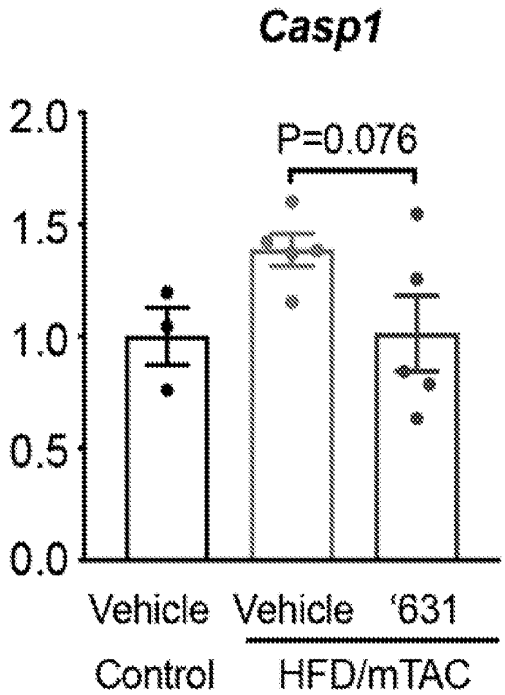

Casp1
2.0
1.5
1.0
0.5
0.0
P=0.076
Vehicle
Vehicle
'631
Control
HFD/mTAC

FIG. 6H

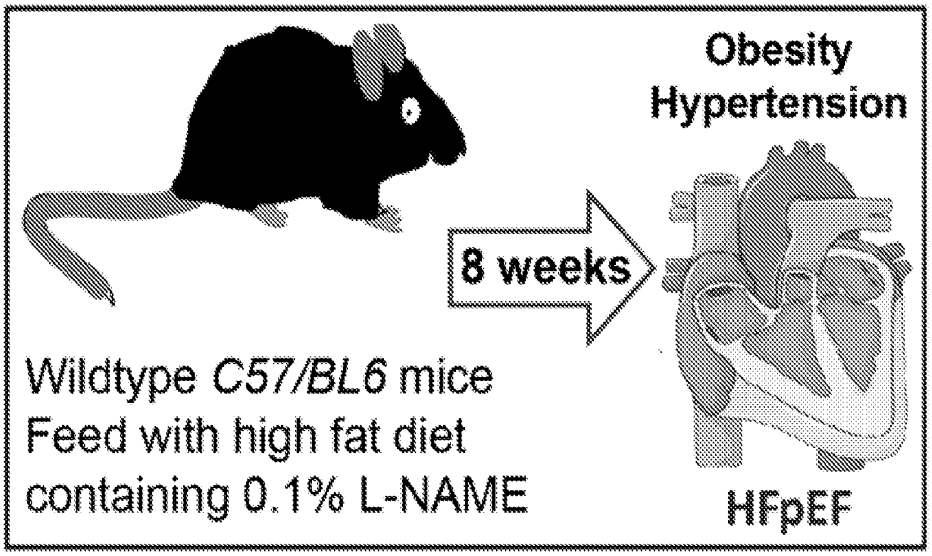

Obesity
Hypertension
8 weeks
Wildtype C57/BL6 mice
Feed with high fat diet
containing 0.1% L-NAME
HFpEF

FIG. 7A

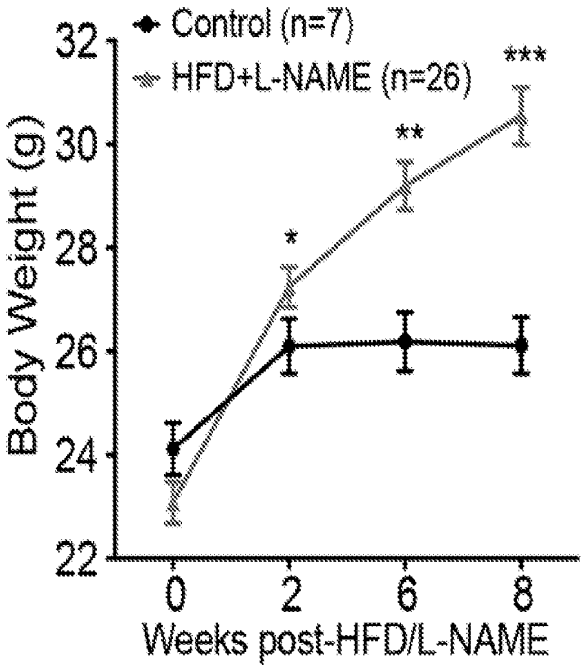

Control (n=7)
HFD+L-NAME (n=26)
Body Weight (g)
32
30
28
26
24
22
*
**
***
0
2
6
8
Weeks post-HFD/L-NAME

FIG. 7B

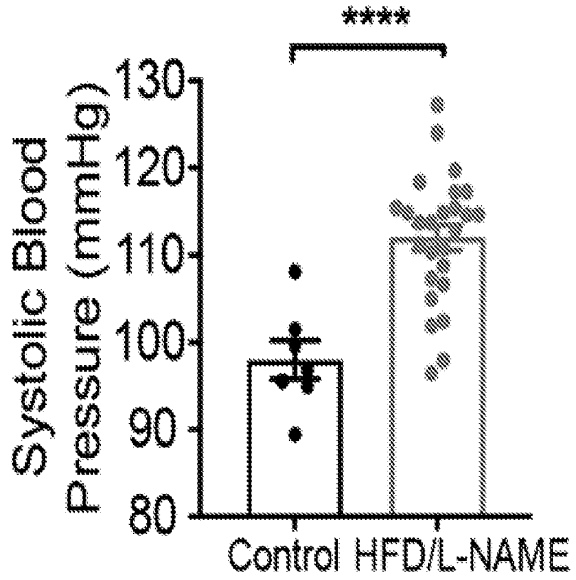

****
Systolic Blood Pressure (mmHg)
130
120
110
100
90
80
Control
HFD/L-NAME

FIG. 7C

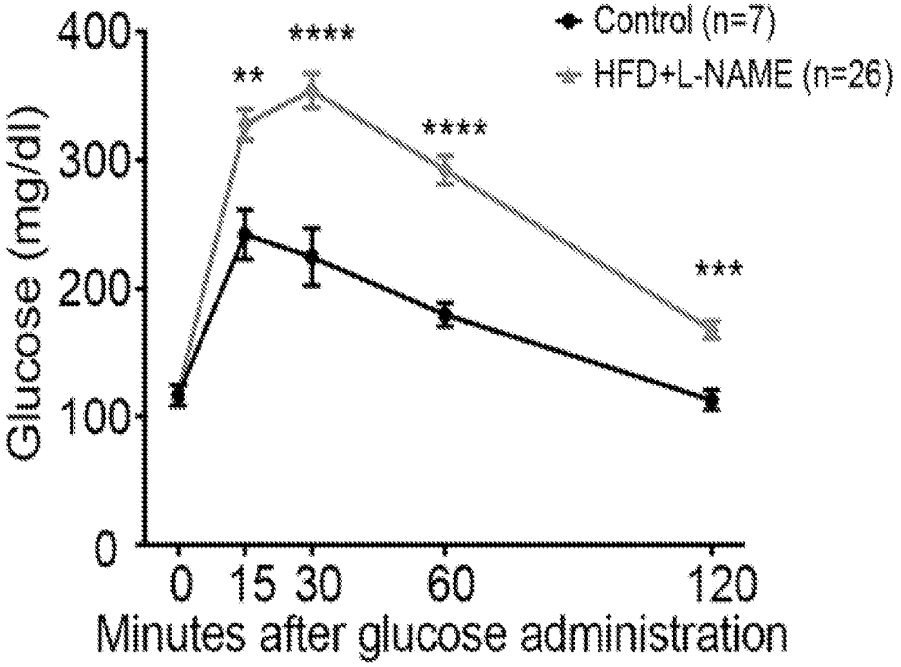

Control (n=7)
HFD+L-NAME (n=26)
Glucose (mg/dl)
400
300
200
100
0
**
****
****
***
0 15 30 60 120
Minutes after glucose administration

FIG. 7D

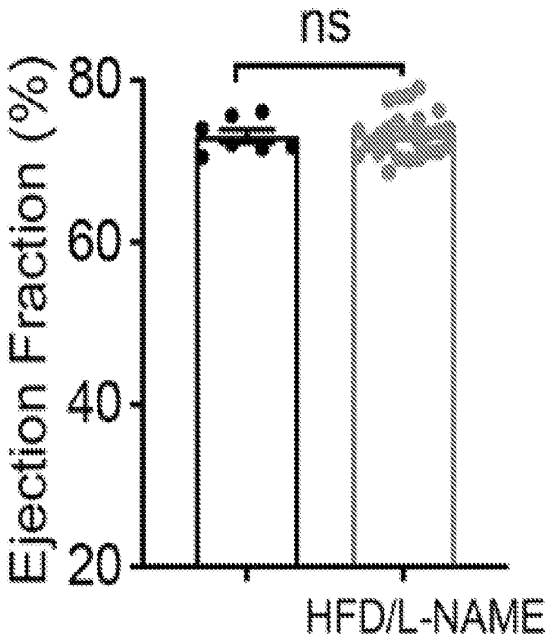

ns
Ejection Fraction (%)
80
60
40
20
HFD/L-NAME

FIG. 7E

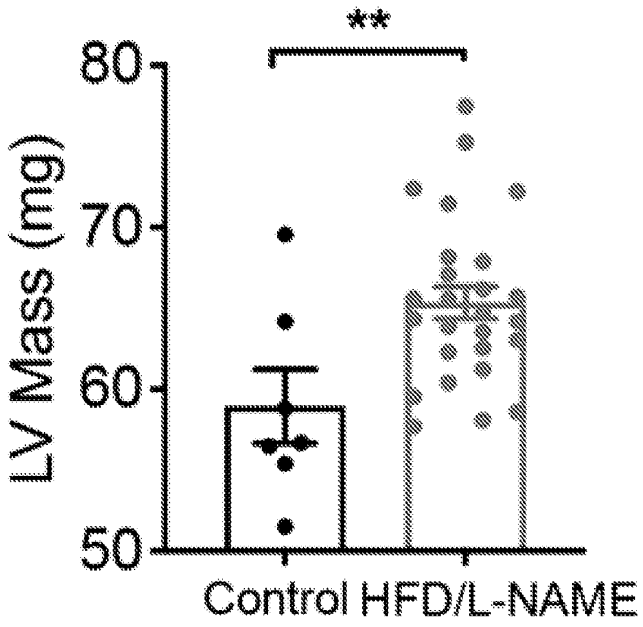

**
80
70
60
50
LV Mass (mg)
Control HFD/L-NAME

FIG. 7F

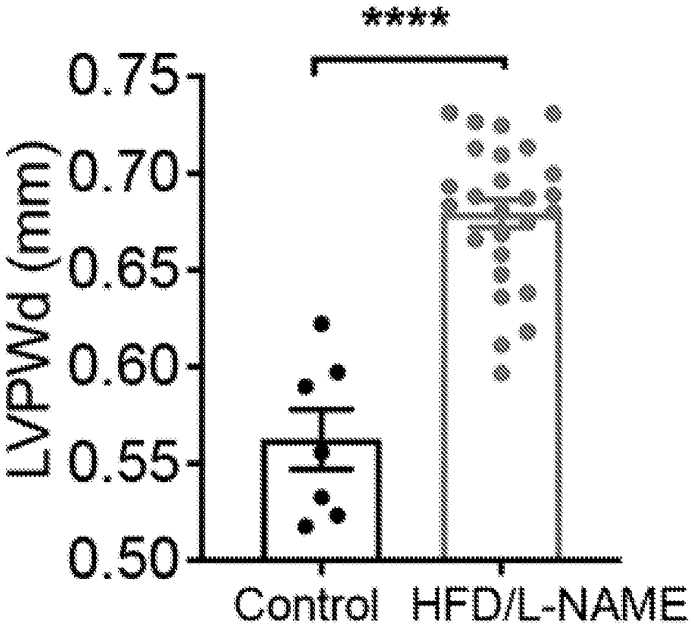

****
0.75
0.70
0.65
0.60
0.55
0.50
LVPWd (mm)
Control HFD/L-NAME

FIG. 7G

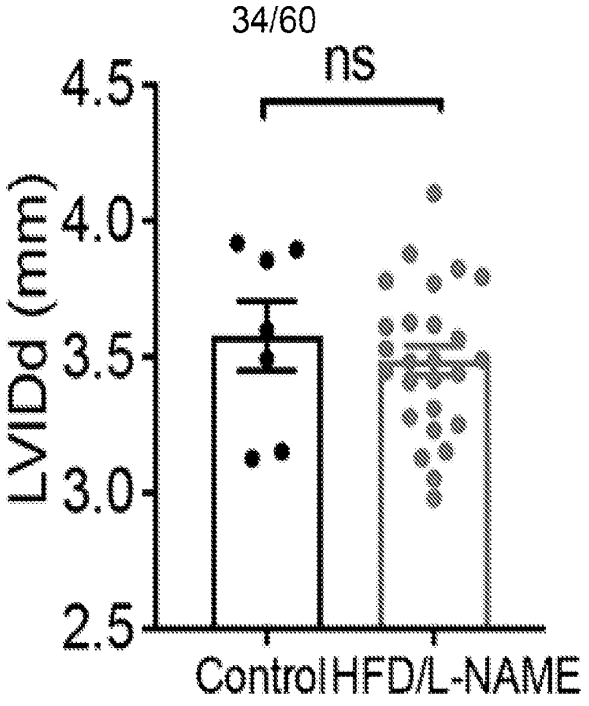

ns
4.5
4.0
3.5
3.0
2.5
LVIDd (mm)
Control
HFD/L-NAME

FIG. 7H

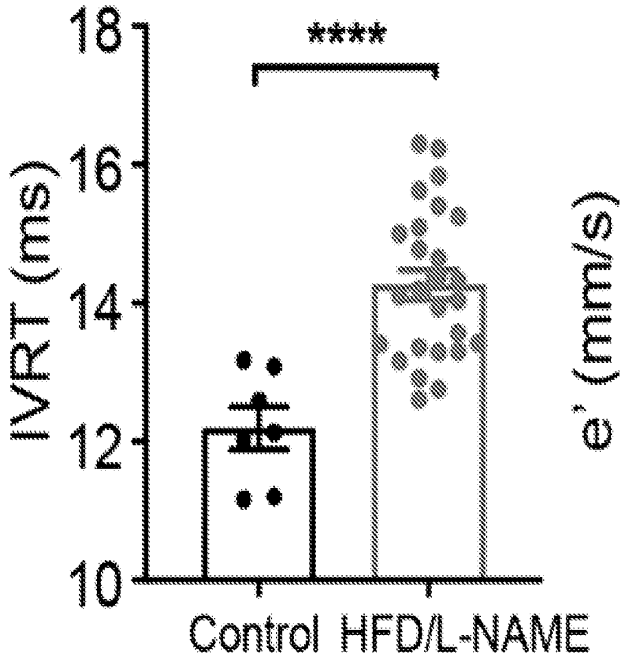

****
18
16
14
12
10
IVRT (ms)
e' (mm/s)
Control
HFD/L-NAME

FIG. 7I

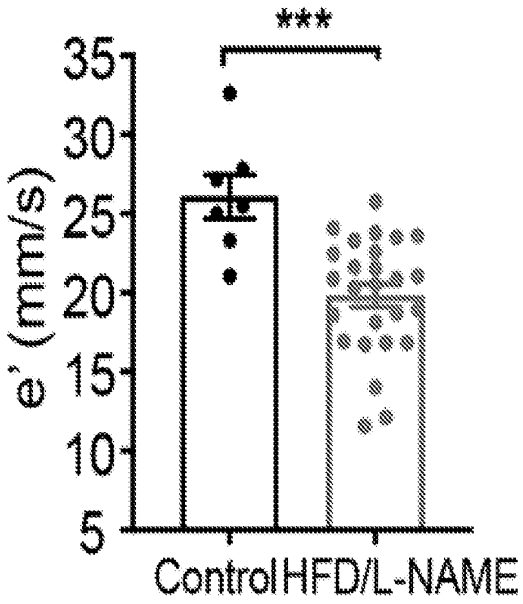

***
35
30
25
20
15
10
5
e' (mm/s)
Control
HFD/L-NAME

FIG. 7J

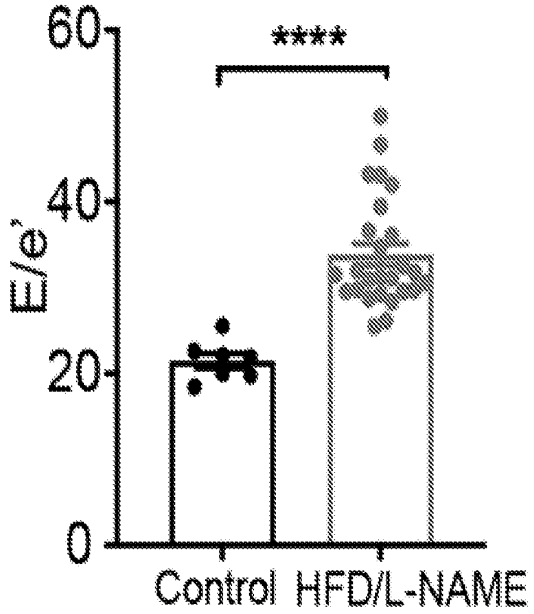

****
60
40
20
0
E/e'
Control
HFD/L-NAME

FIG. 7K

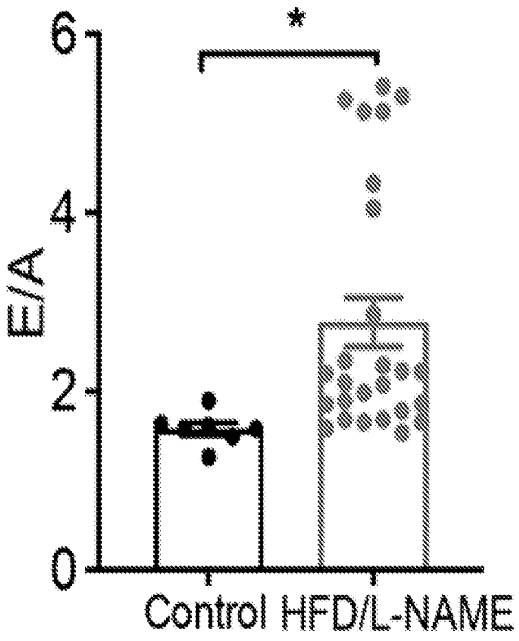


FIG. 7L

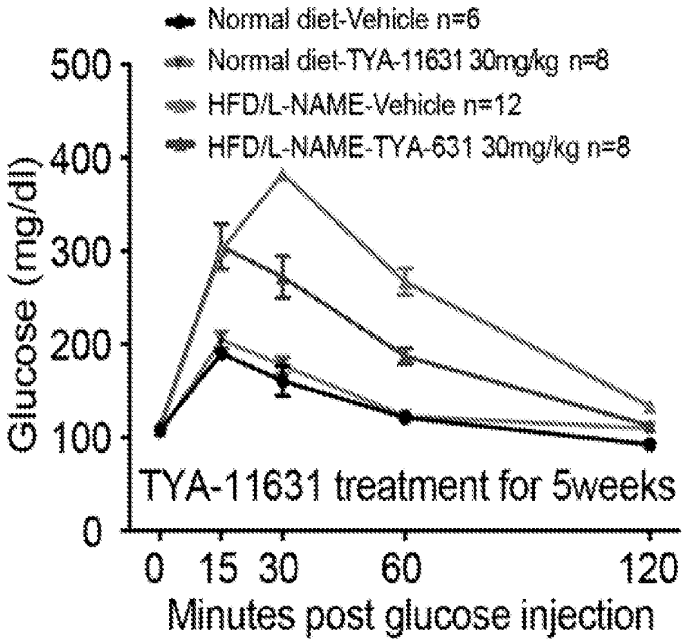

Normal diet-Vehicle n=6
Normal diet-TYA-11631 30mg/kg n=8
HFD/L-NAME-Vehicle n=12
HFD/L-NAME-TYA-631 30mg/kg n=8
Glucose (mg/dl)
500
400
300
200
100
0
TYA-11631 treatment for 5weeks
0 15 30 60 120
Minutes post glucose injection

FIG. 8A

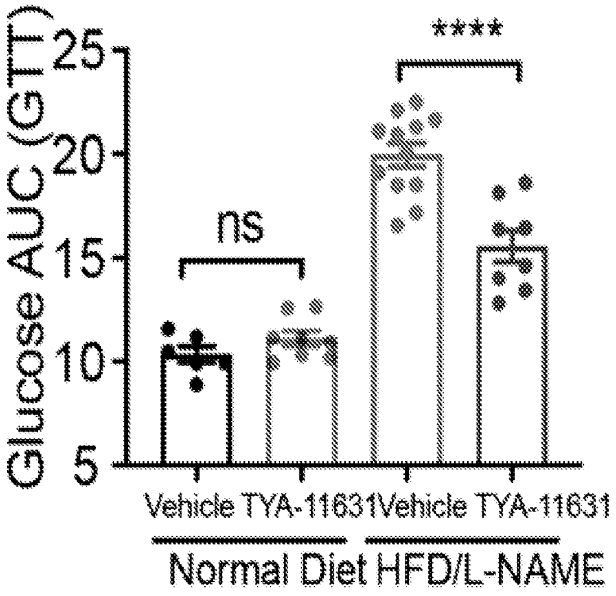

Glucose AUC (GTT)
25
20
15
10
5
****
ns
Vehicle TYA-11631Vehicle TYA-11631
Normal Diet HFD/L-NAME

FIG. 8B

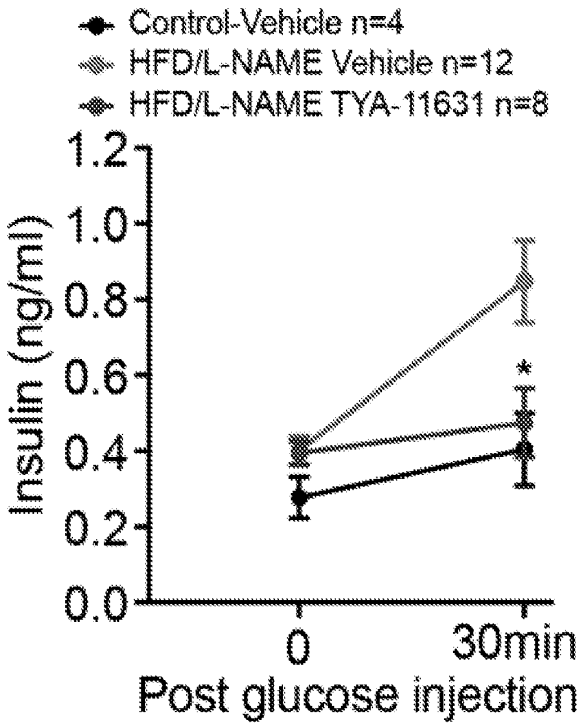

Control-Vehicle n=4
HFD/L-NAME Vehicle n=12
HFD/L-NAME TYA-11631 n=8
Insulin (ng/ml)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
*
0
30min
Post glucose injection

FIG. 8C

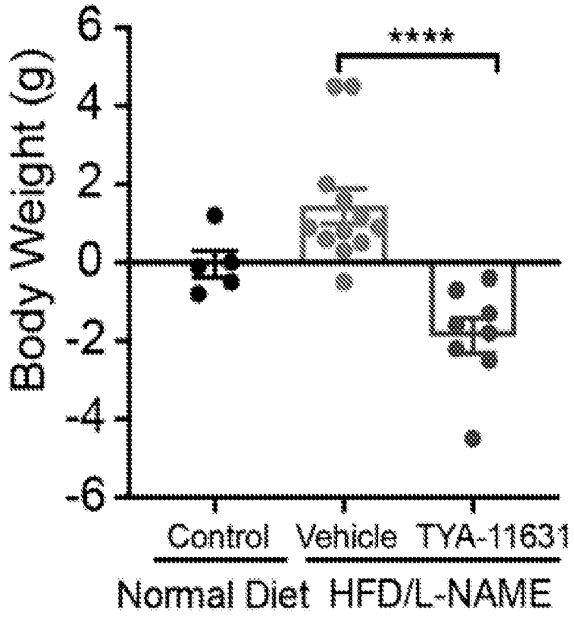

Body Weight (g)
6
4
2
0
-2
-4
-6
****
Control
Vehicle
TYA-11631
Normal Diet
HFD/L-NAME

FIG. 8D

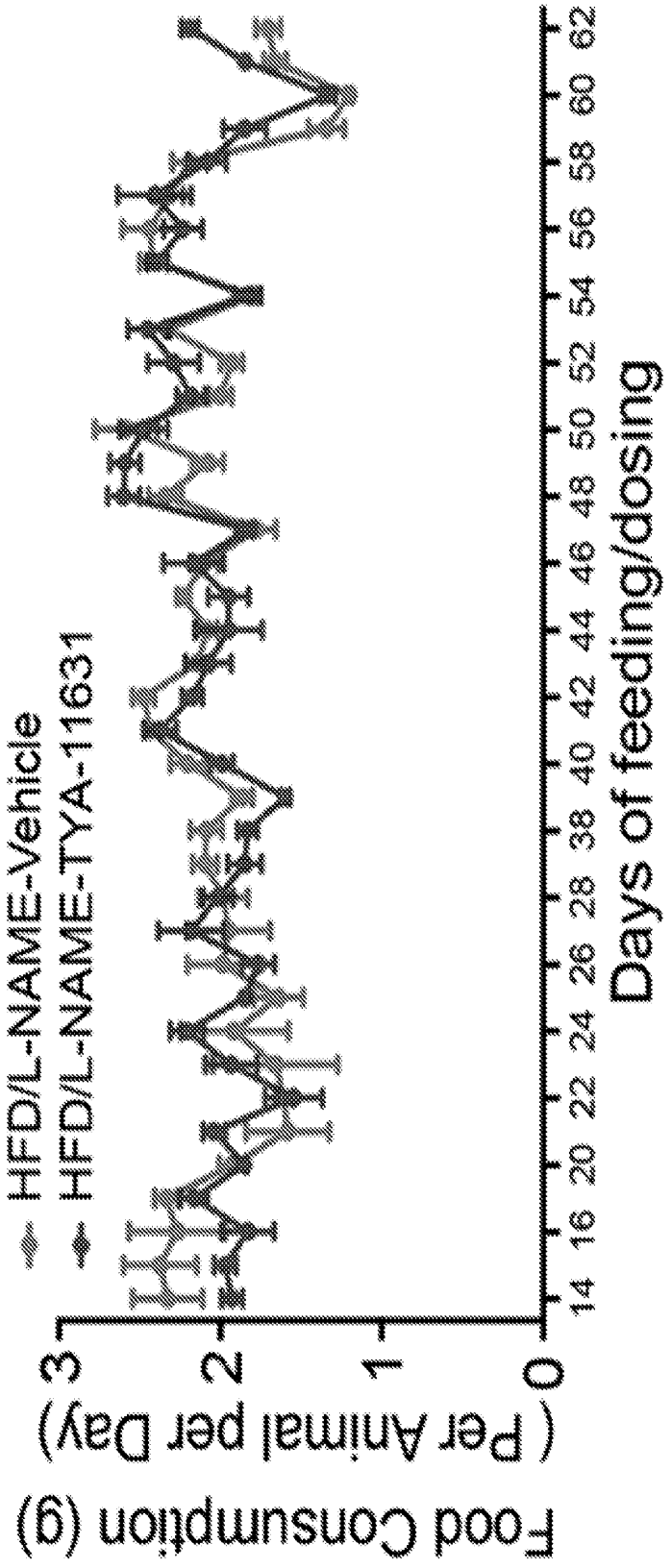

HFD/L-NAME-Vehicle
HFD/L-NAME-TYA-11631
Food Consumption (g)
(Per Animal per Day)
0
1
2
3
14 16 20 22 24 26 28 38 40 42 44 46 48 50 52 54 56 58 60 62
Days of feeding/dosing

FIG. 8E

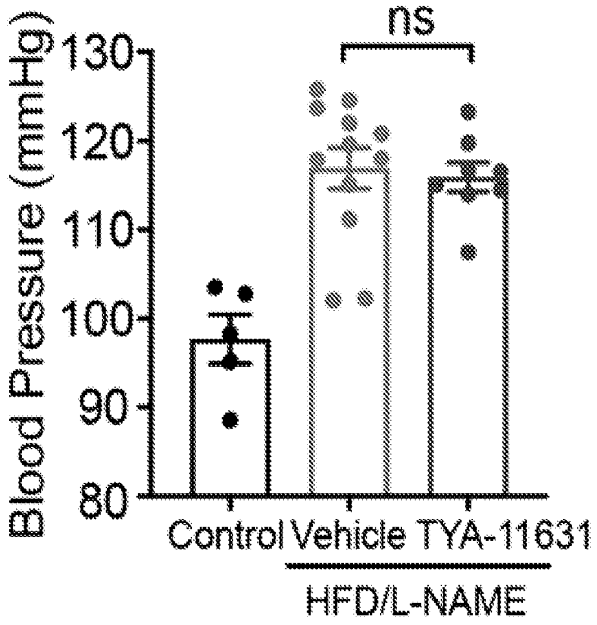

ns
Blood Pressure (mmHg)
130
120
110
100
90
80
Control
Vehicle
TYA-11631
HFD/L-NAME

FIG. 8F

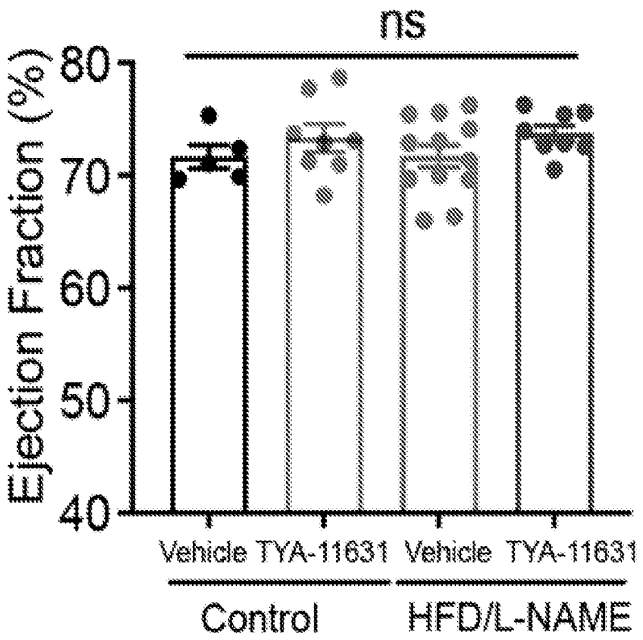

ns
Ejection Fraction (%)
80
70
60
50
40
Vehicle
TYA-11631
Vehicle
TYA-11631
Control
HFD/L-NAME

FIG. 8G

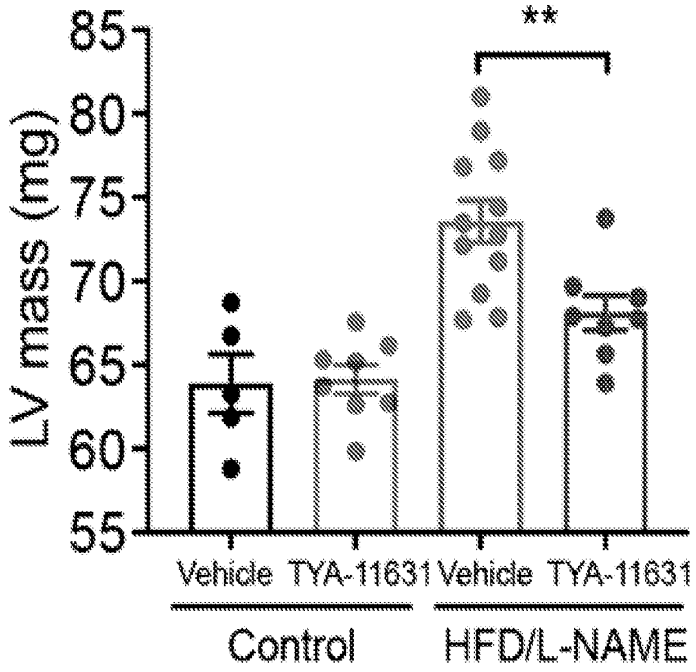

**
LV mass (mg)
85
80
75
70
65
60
55
Vehicle
TYA-11631
Vehicle
TYA-11631
Control
HFD/L-NAME

FIG. 8H

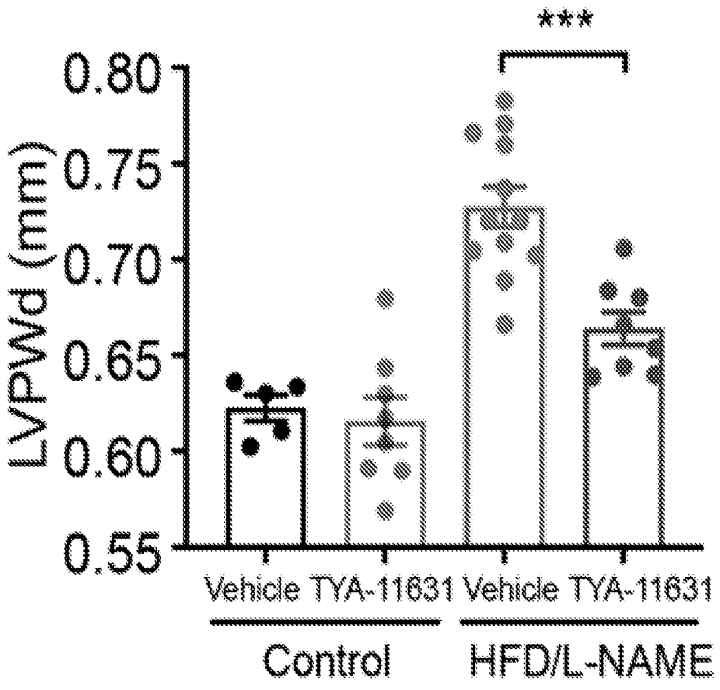

***
LVPWd (mm)
0.80
0.75
0.70
0.65
0.60
0.55
Vehicle
TYA-11631
Vehicle
TYA-11631
Control
HFD/L-NAME

FIG. 8I

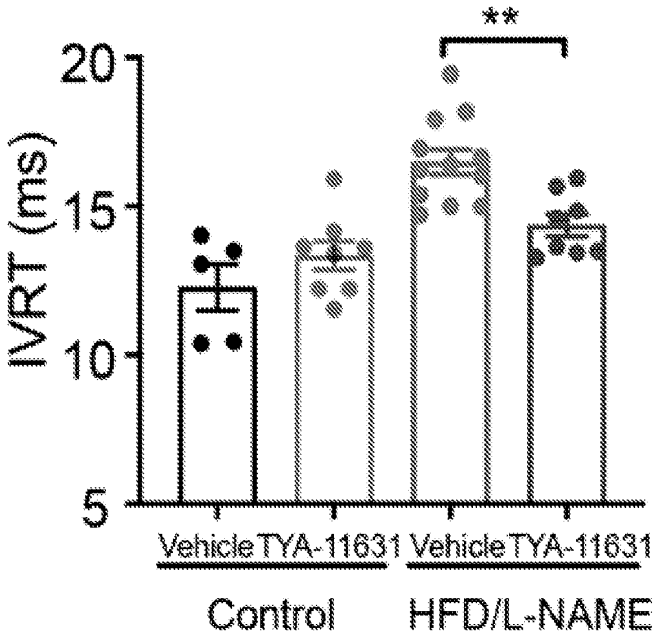

**
IVRT (ms)
20
15
10
5
Vehicle
TYA-11631
Vehicle
TYA-11631
Control
HFD/L-NAME

FIG. 8J

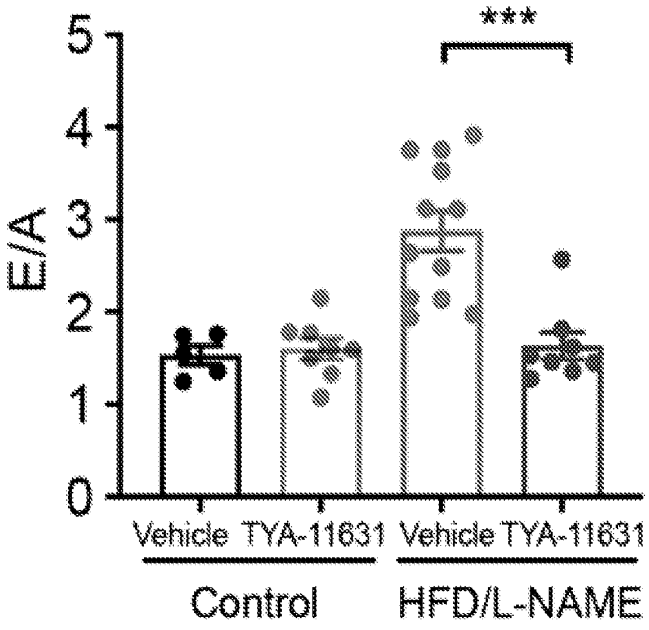

***
E/A
5
4
3
2
1
0
Vehicle
TYA-11631
Vehicle
TYA-11631
Control
HFD/L-NAME

FIG. 8K

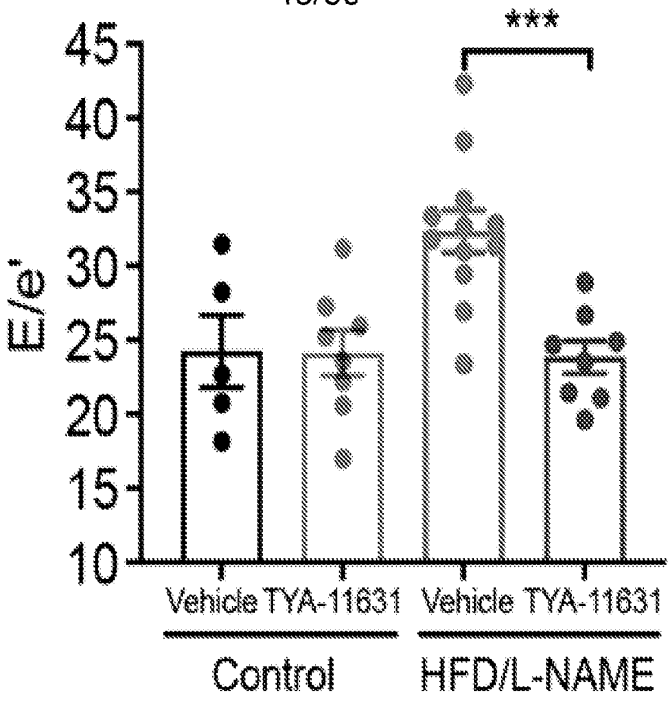

***
E/e'
45
40
35
30
25
20
15
10
Vehicle
TYA-11631
Vehicle
TYA-11631
Control
HFD/L-NAME

FIG. 8L

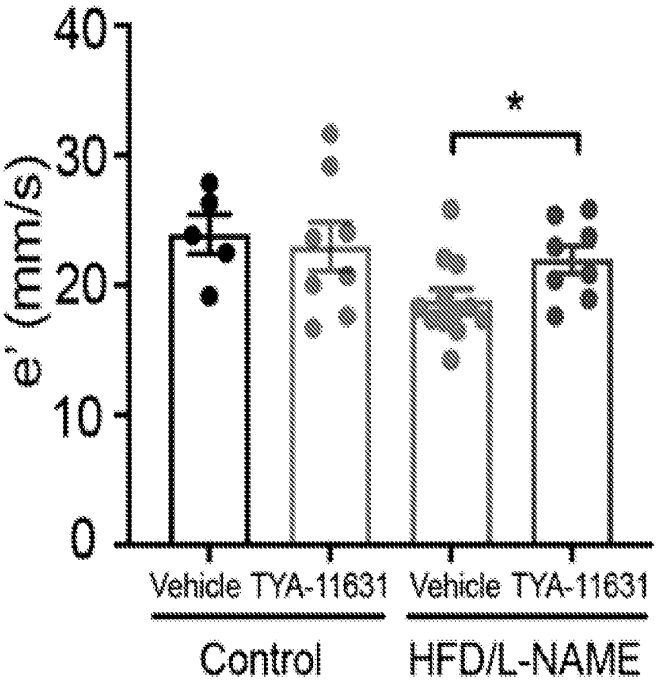

*
e' (mm/s)
40
30
20
10
0
Vehicle
TYA-11631
Vehicle
TYA-11631
Control
HFD/L-NAME

FIG. 8M

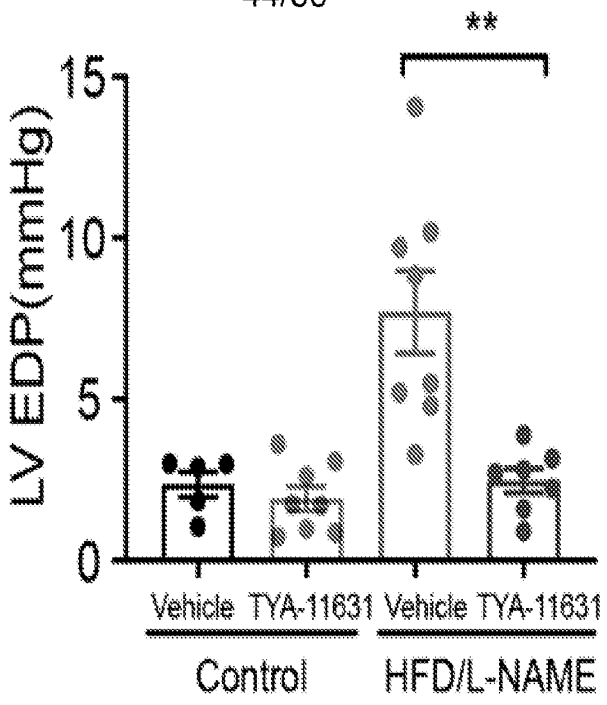

**
LV EDP(mmHg)
15
10
5
0
Vehicle
TYA-11631
Vehicle
TYA-11631
Control
HFD/L-NAME

FIG. 8N

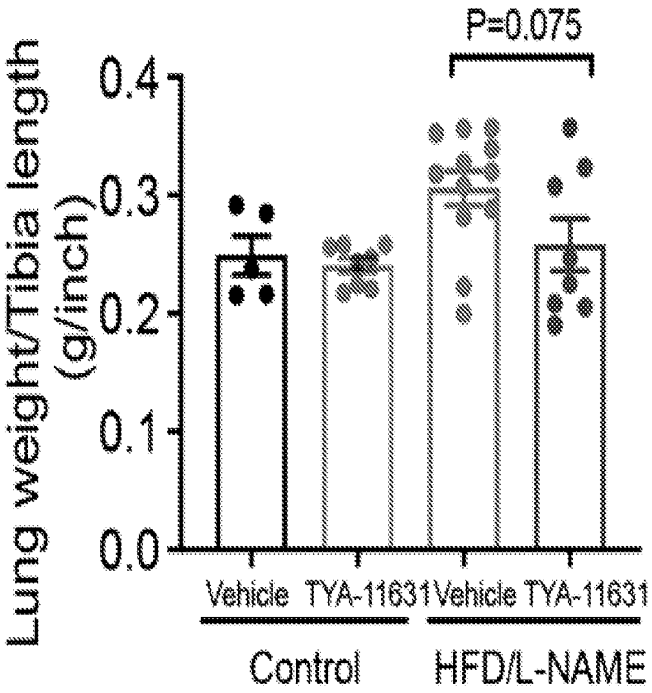

P=0.075
Lung weight/Tibia length (g/inch)
0.4
0.3
0.2
0.1
0.0
Vehicle
TYA-11631
Vehicle
TYA-11631
Control
HFD/L-NAME

FIG. 8O

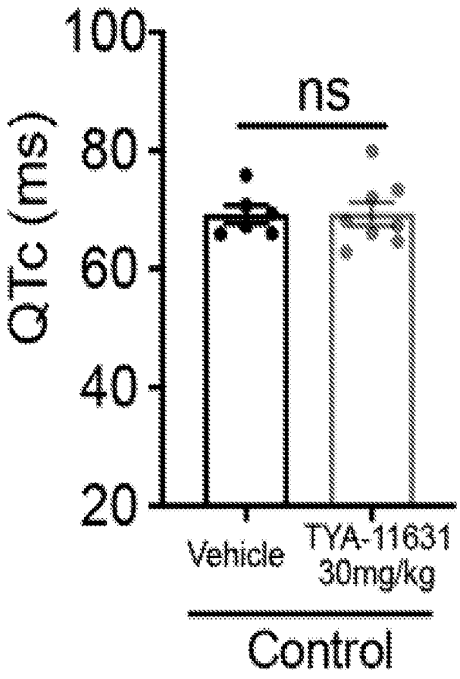

100
80
60
40
20
QTc (ms)
ns
Vehicle
TYA-11631
30mg/kg
Control

FIG. 8P

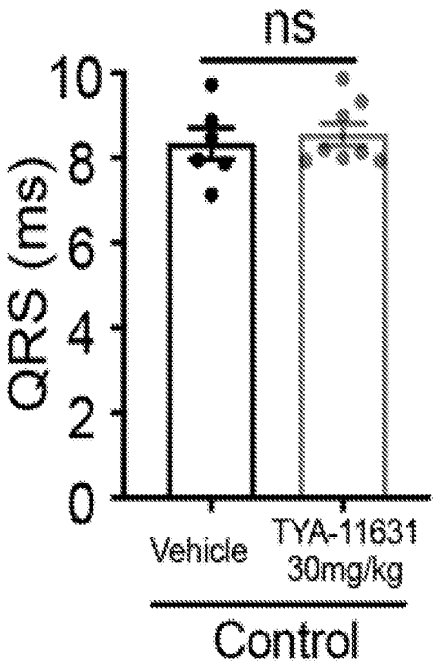

10
8
6
4
2
0
QRS (ms)
ns
Vehicle
TYA-11631
30mg/kg
Control

FIG. 8Q

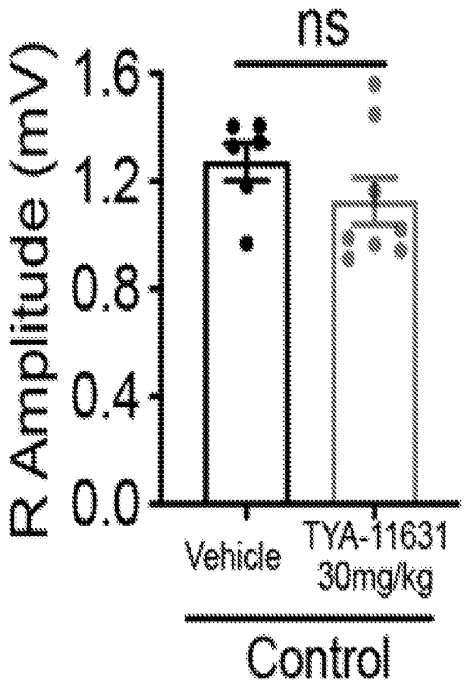

ns
R Amplitude (mV)
1.6
1.2
0.8
0.4
0.0
Vehicle
TYA-11631
30mg/kg
Control

FIG. 8R

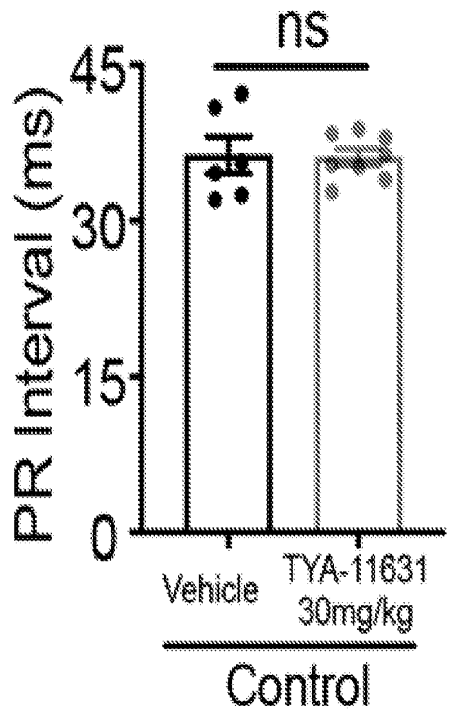
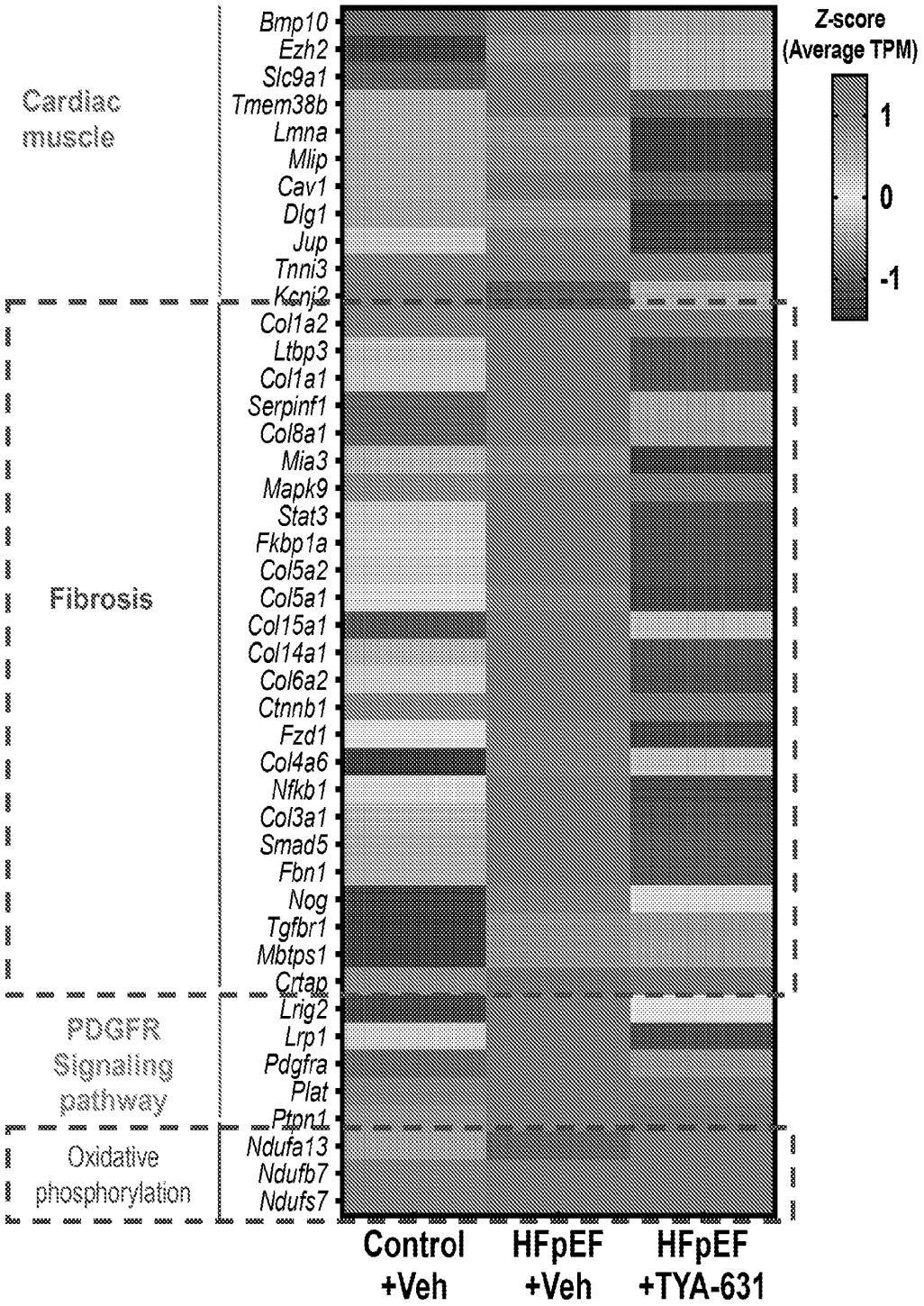

ns
PR Interval (ms)
45
30
15
0
Vehicle
TYA-11631
30mg/kg
Control

FIG. 8S



Only genes with significant expression differences in each GO and WP gene set are shown

FIG. 9

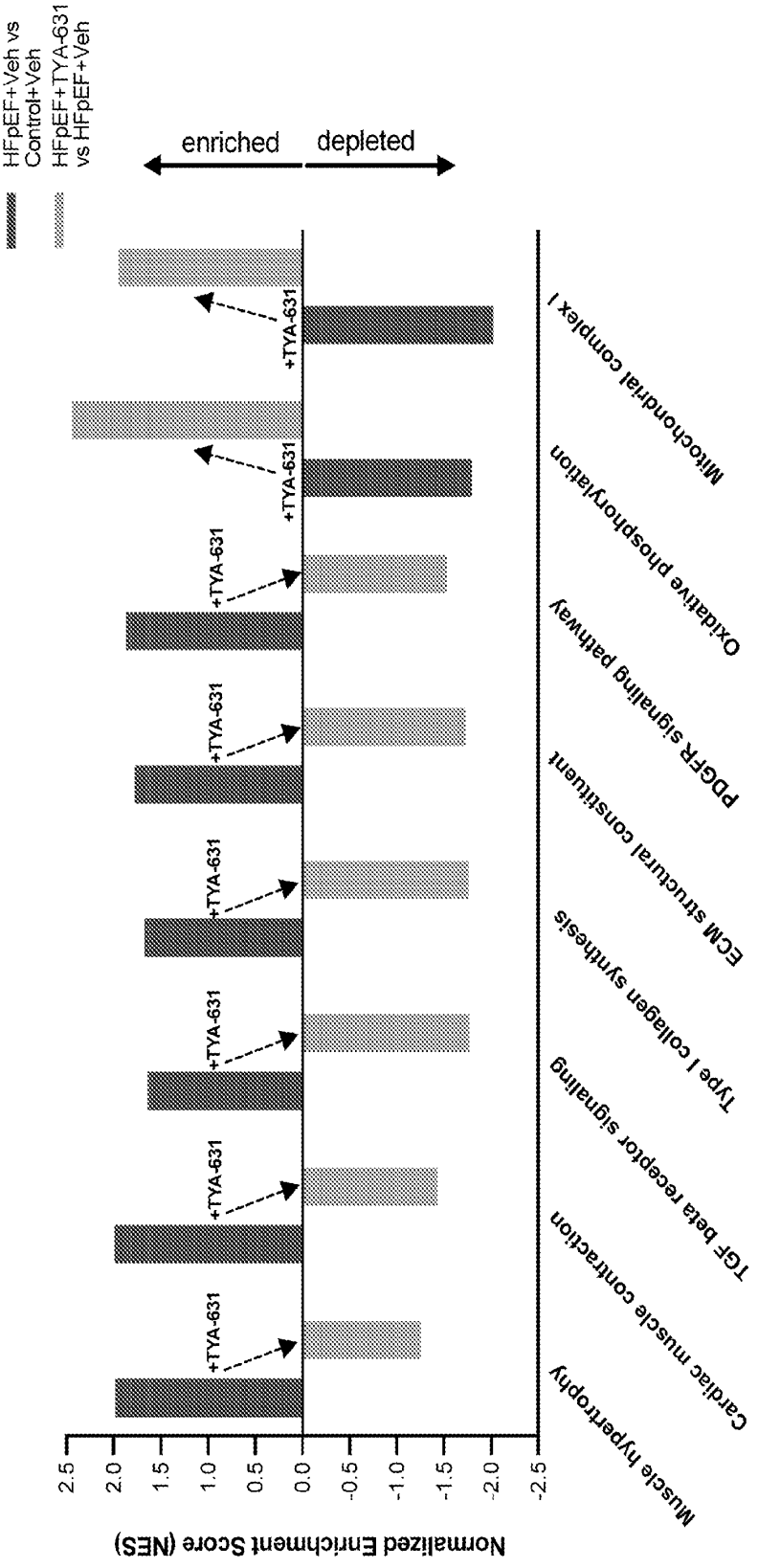

HFpEF+Veh vs Control+Veh
HFpEF+TYA-631 vs HFpEF+Veh
enriched
depleted
+TYA-631
Mitochondrial complex I
Oxidative phosphorylation
PDGFR signaling pathway
ECM structural constituent
Type I collagen synthesis
TGF beta receptor signaling
Cardiac muscle contraction
Muscle hypertrophy
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
Normalized Enrichment Score (NES)

FIG. 10

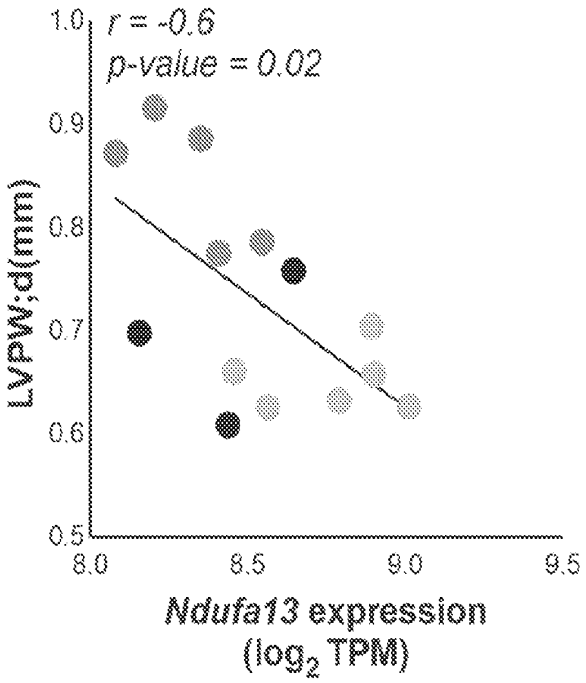


FIG. 11A

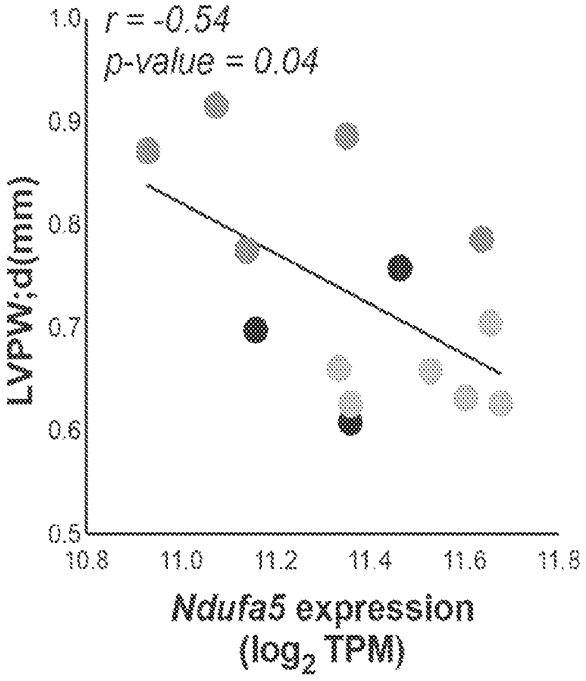


FIG. 11B

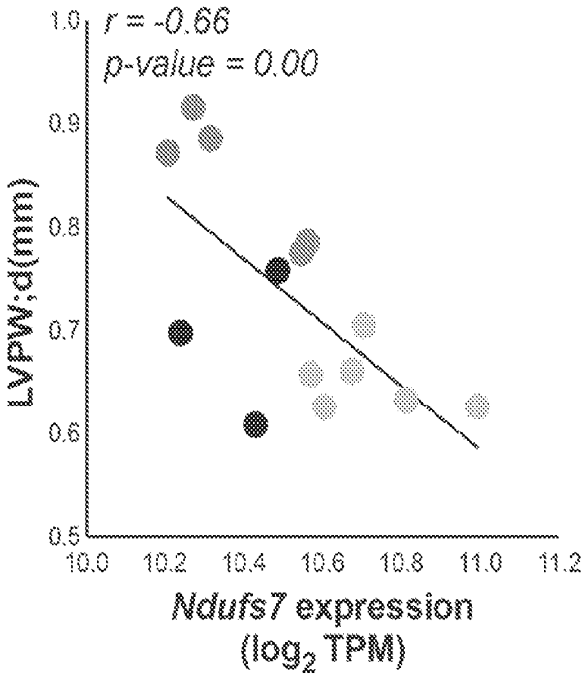


FIG. 11C

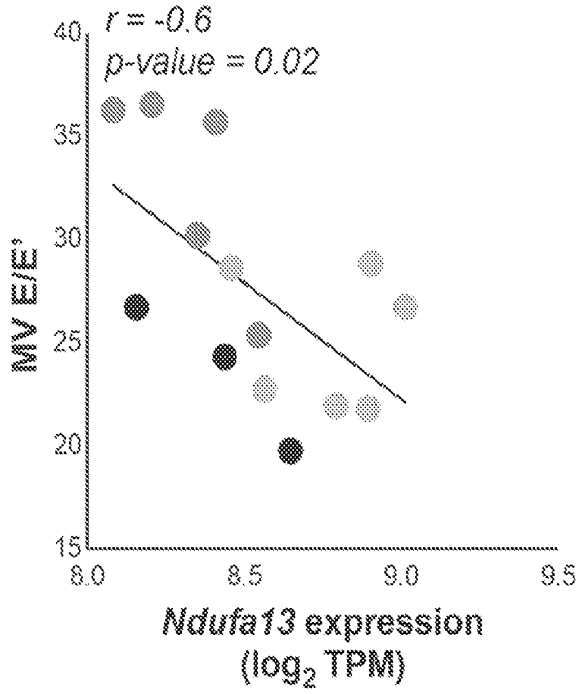


FIG. 11D

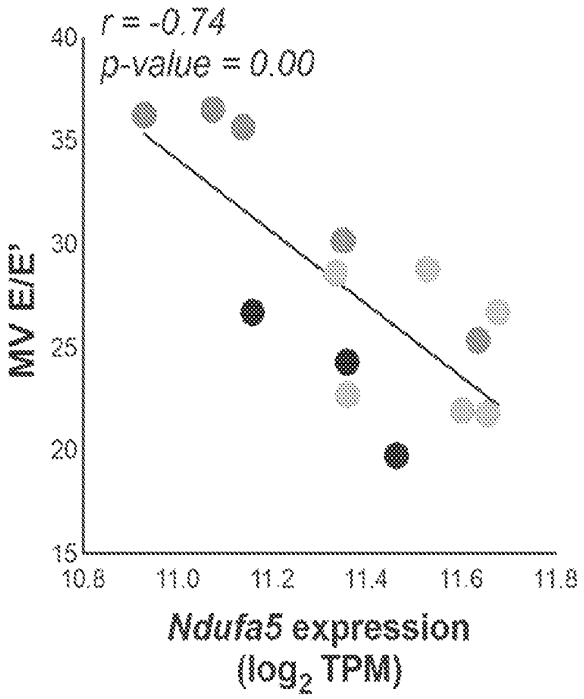


FIG. 11E

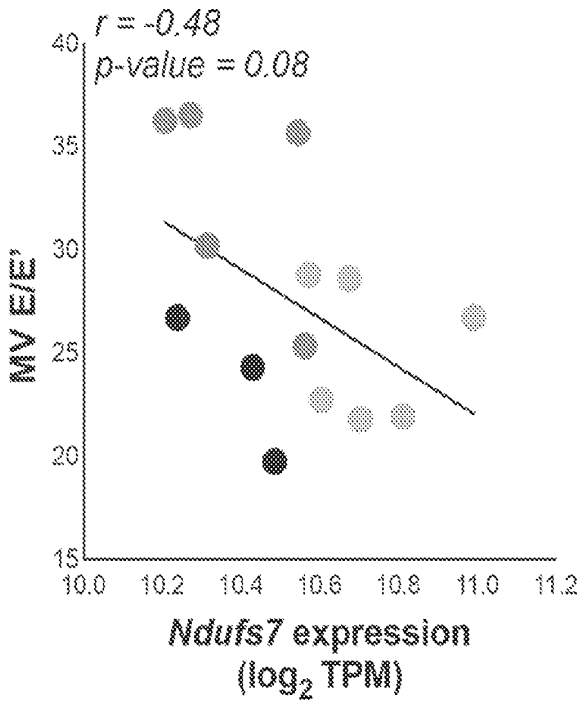


FIG. 11F

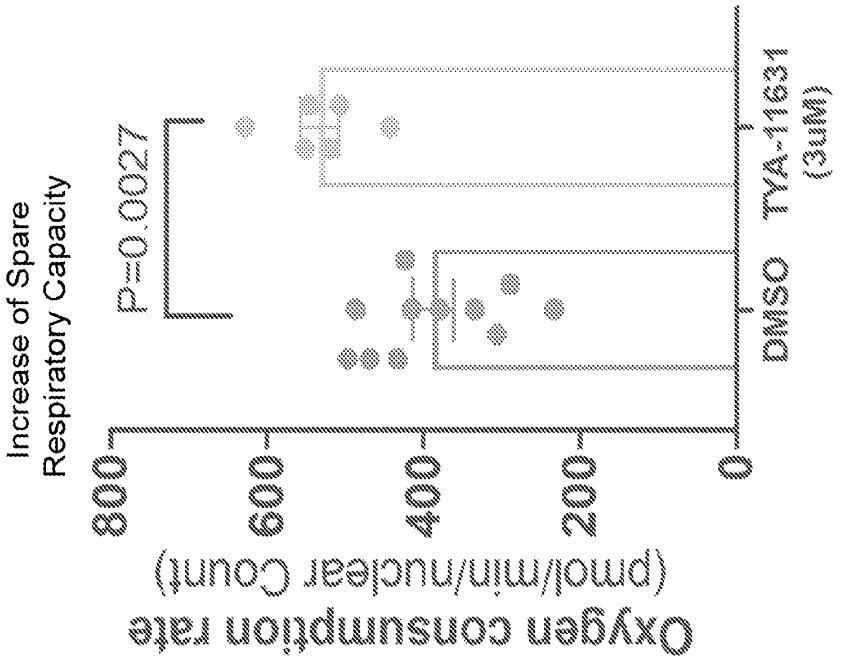


FIG. 11H

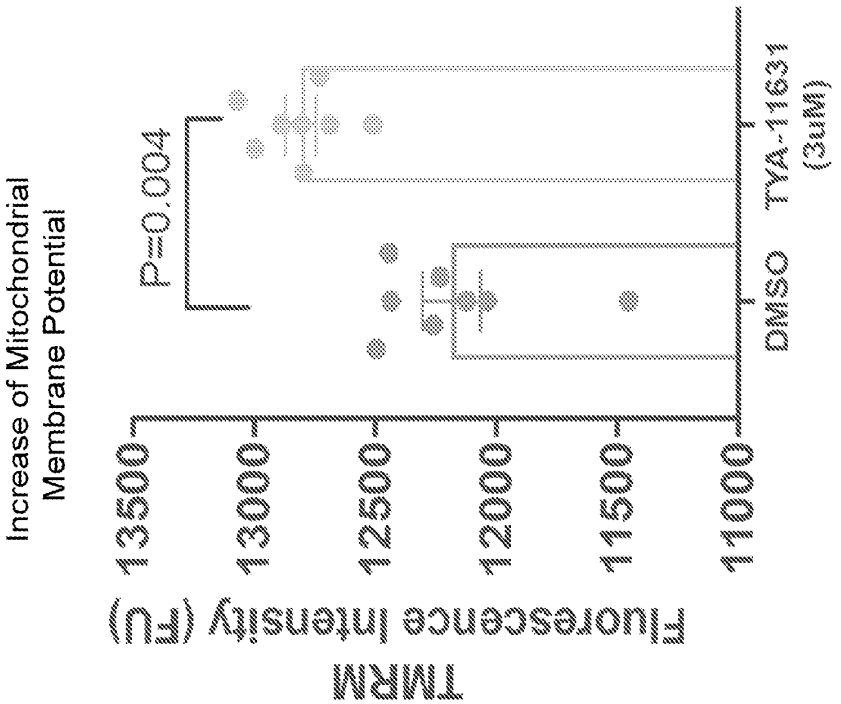


FIG. 11G

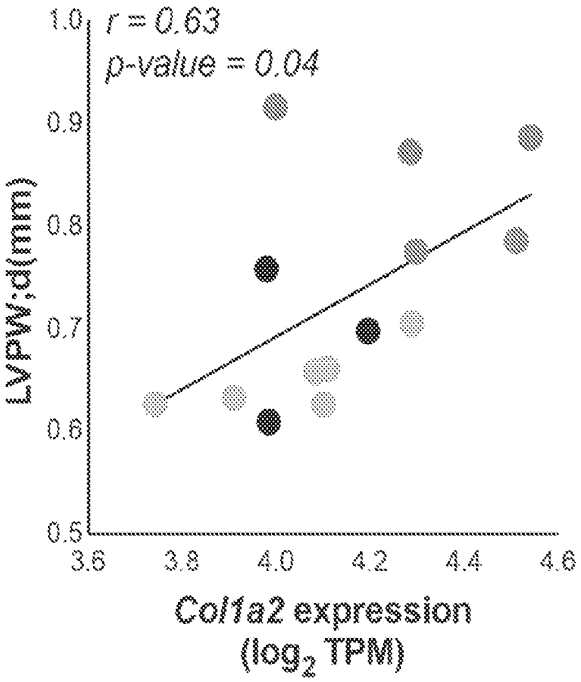


FIG. 12A

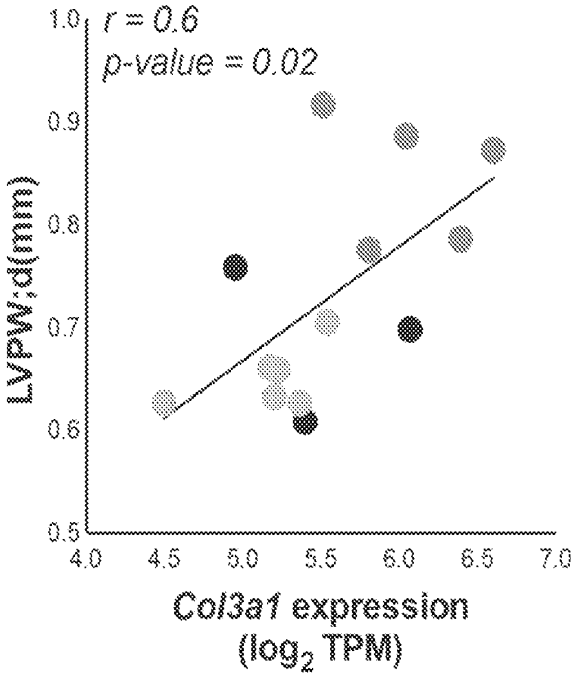


FIG. 12B

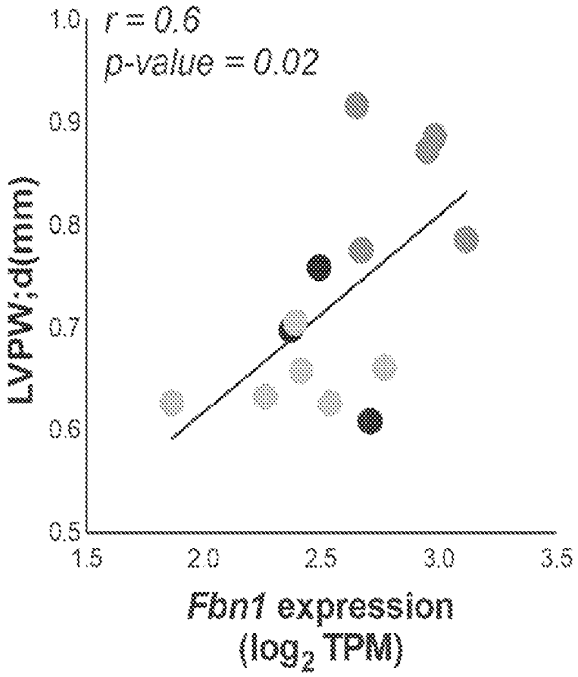


FIG. 12C

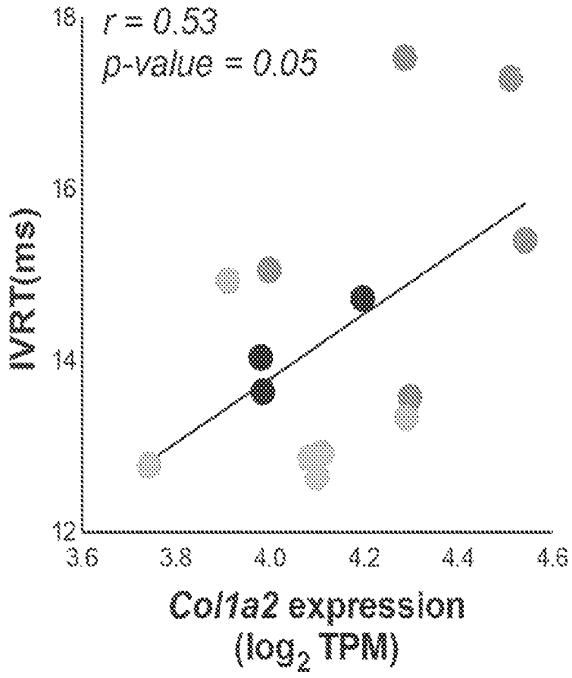


FIG. 12D

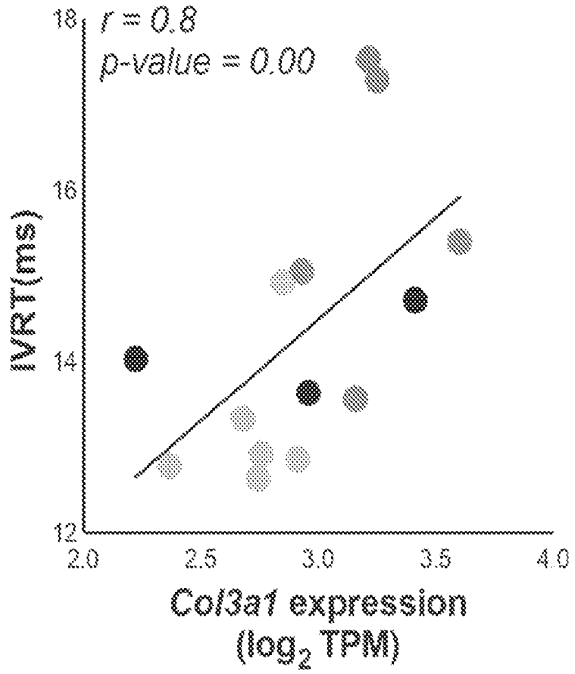


FIG. 12E

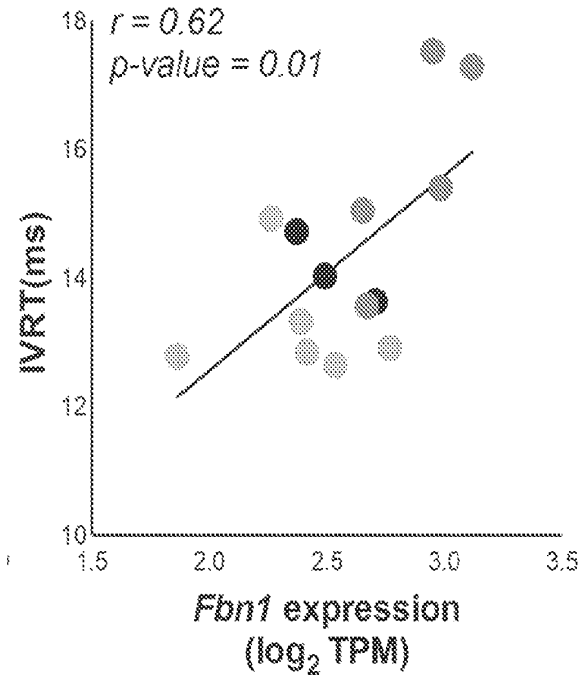


FIG. 12F

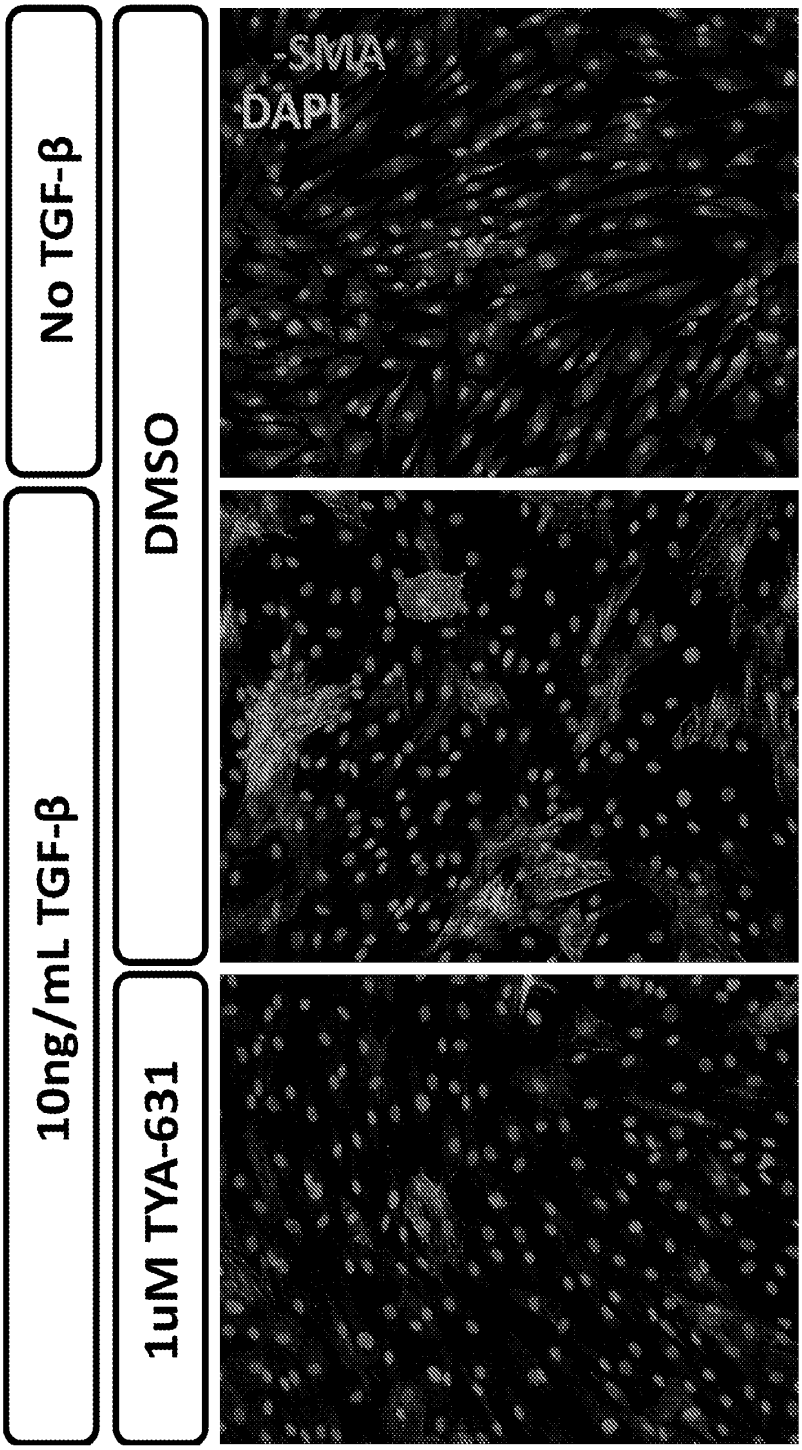


FIG. 13A

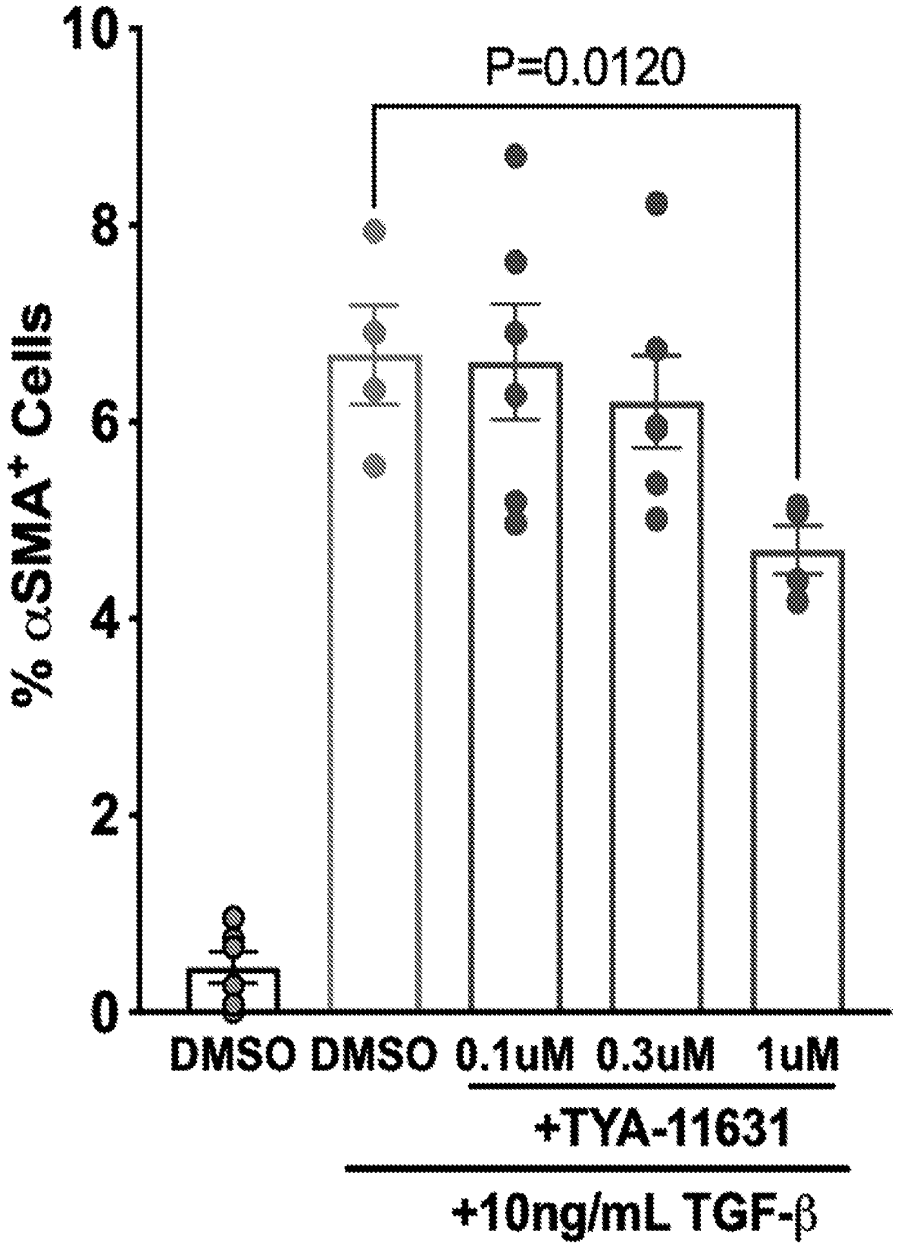

P=0.0120
% αSMA+ Cells
10
8
6
4
2
0
DMSO
DMSO
0.1uM
0.3uM
1uM
+TYA-11631
+10ng/mL TGF-β

FIG. 13B

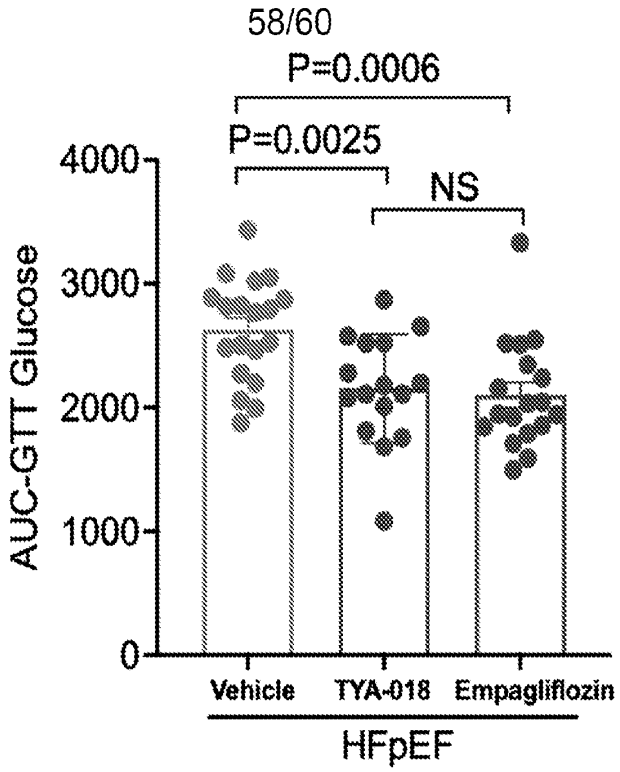


FIG. 14A

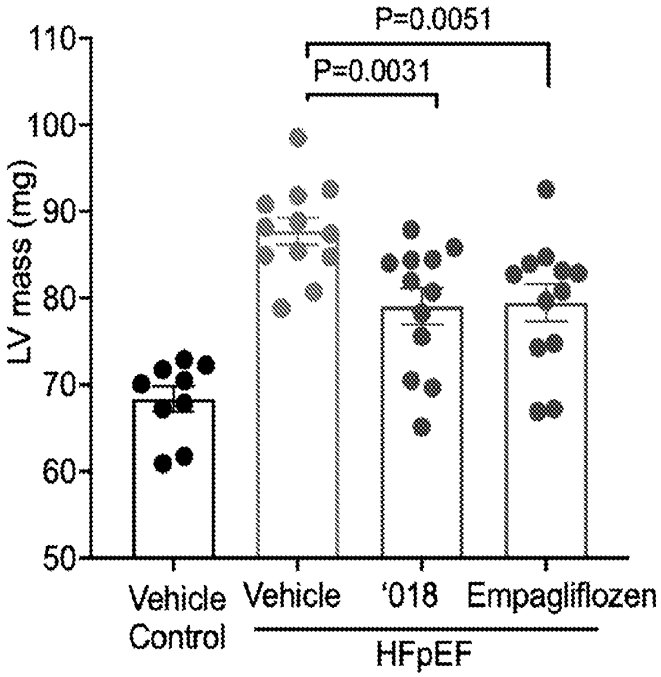


FIG. 14B

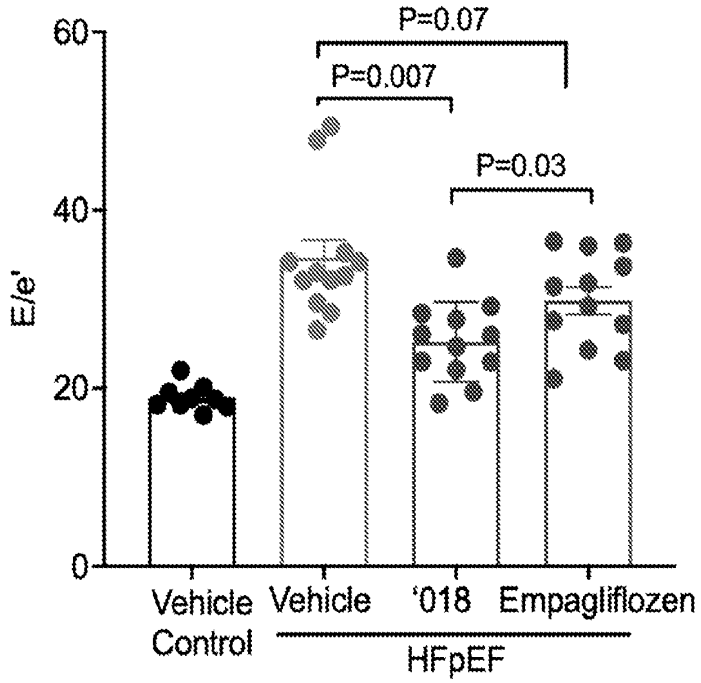


FIG. 14C

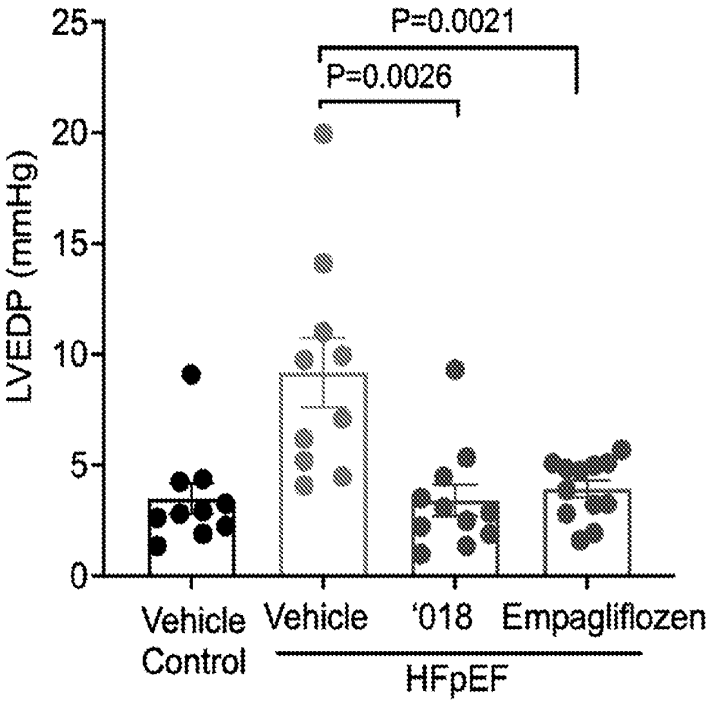


FIG. 14D

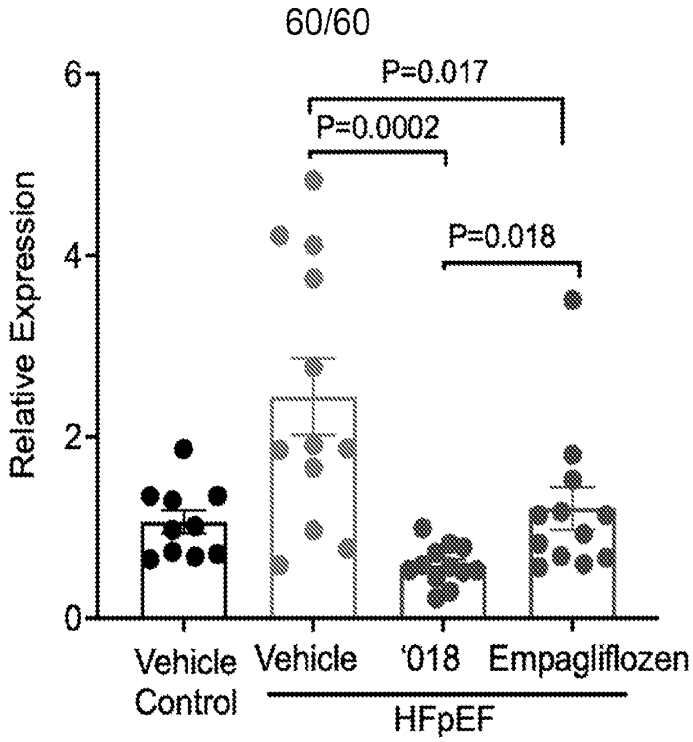


FIG. 14E

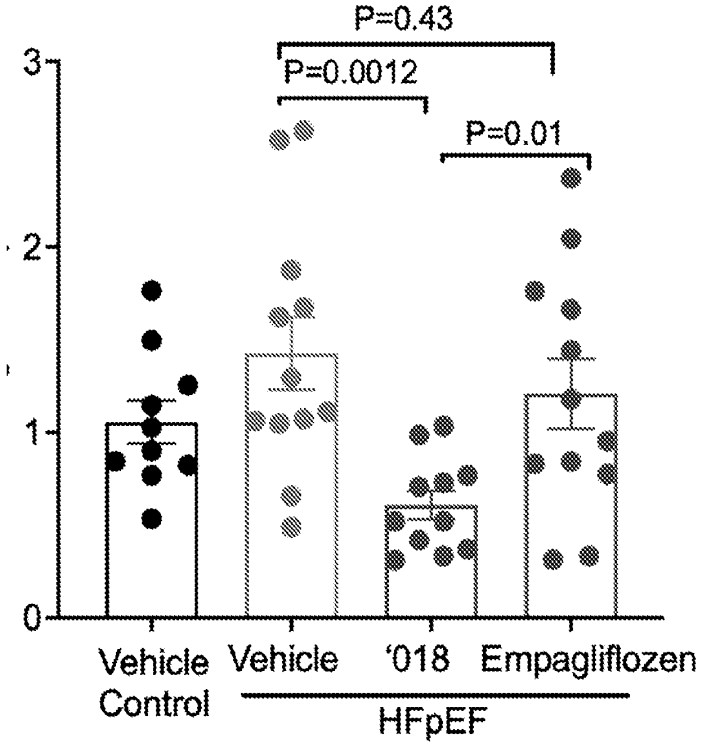


FIG. 14F