**Clinical Experience with Intravenous Angiotensin II Administration:
A Systematic Review of Safety**

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**SUPPLEMENTAL DIGITAL CONTENT 2**

**Pressor Responses to Angiotensin II in Representative Studies with Cardiovascular Focus**

**Pressor Responses to Angiotensin II in Representative Studies with Cardiovascular Focus**

|  |  |  |  | **Increase in Pressure, mmHg (Percentage)c** |
| --- | --- | --- | --- | --- |
| **1st Author & Year** | **Study/Dose Typea** | **Subjects (N)** | **IV Doseb (duration)** | **MAP** | **SBP** | **DBP** |
| Ahmed 1975 | 2 groups/target | Normal (5) | ~3 µg/min (10 min) | 27 (30%) | -- | 21 (29%) |
|  |  | Diffuse myocardial disease (6) | ~3 µg/min (10 min) | 26 (27%) | -- | 20 (26%) |
| Berman 1971 | 1 group/fixed  | Benign HTN (8), ESRD/dialysis (2) | 1.25 µg (bolus) (n=7)d | -- | 49 (30%) | 29 (37%) |
|  |  |  | 2.5 µg (bolus) (n=2)d | -- | 55 (40%) | 30 (46%) |
|  |  |  | 5 µg (bolus) (n=2) | -- | 50 (30%) | 25 (28%) |
| Bianco 1980 | 2 groups/target | Normal (6) | 1-3 µg/min (--) | -- | 59 (50%) | -- |
|  |  | CAD, after exercise (10) |  | -- | 44 (34%) | -- |
| Brod 1969 | 1 group/target | Normotensive (9)e  | 3.6 µg/min (3×10 min) | 34 (36%) | -- | -- |
| Cachovan 1976 | 1 group/target | Normotensive (10) | 0.12-5.0 µg/min (20 min) | 29 (31%) | -- | -- |
| Cargill 1994 | 1 group/incremental | Normal (7) | 2 ng/kg/min (30 min) | 10 (12%) | 11 (9%) | 11 (16%) |
|  |  |  | 4 ng/kg/min (30 min) | 19 (23%) | 21 (18%) | 19 (28%) |
|  |  |  | 6 ng/kg/min (30 min) | 27 (32%) | 34 (29%) | 25 (37%) |
| Cohn 1965 | 1 group/target | Hypotensive, various etiologies (28) | 14.1 µg/min, range 0.3-60 µg/min (duration NR) | 25 (48%) | -- | -- |
| Elliott 1988 | 1 group/target | eHTN (9) | PD25=5.3 ± 1.8 ng/kg/min(2.5-10.0 ng/kg/min, 8 min) | 20 (--) | -- | -- |
| Goldsmith 1993 | 1 group/fixed  | CHF (8) | 5 ng/kg/minf (60 min) | 10 (12%) | -- | -- |
| Goldsmith 1994 | 1 group/fixed with 3% NaCl | Healthy (13) | 2 ng/kg/min (120 min) | 8 (9%) | -- | -- |
| Greenfield 1968 | 1 group/fixed | Male patients 10-20 days after subtotal resection of brain tumor (8) | 1 µg/min (5 min) | 25 (25%) | 35 (27%) | 20 (24%) |
| Henning 1967 | 1 group/target | Healthy (5) | 2.2 µg/min (5 min) | 23 (26%) | -- | -- |
| Henriksen 1985 | 1 group/target | Normotensive (10)(2 healthy, 4 with transient cerebral ischemia/cerebrothrombotic episode, 4 with type 1 diabetes) | 0.5-1.0 µg/min (45 min) BP measured at 25 min  BP measured at 40 min | 28 (29%)31 (32%) | ---- | ---- |
| Johnson 1962 | 1 group, 2 conditions/fixed | Normal, fasting (10) | 50 ng/kg/min (30‑60 min) | 30 (31%) | -- | -- |
|  |  | Normal, exercise (3) |  | 10 (9%) | -- | -- |
| Katayama 1992 | 1 group/fixed | “Old” MI (15) | 20 ng/kg/min (--) |  | 33 (24%)g |  |
| Klingbeil 1999 | 2 groups/incremental | Mild eHTN (30) | 0.5 ng/kg/min (30 min) | 4 (4%) | -- | -- |
|  |  |  | 3.0 ng/kg/min (30 min) | 14 (13%) | -- | -- |
|  |  | Normotensive (30) | 0.5 ng/kg/min (30 min) | 3 (3%) | -- | -- |
|  |  |  | 3.0 ng/kg/min (30 min) | 10 (10%) | -- | -- |
| Larsson 1999 | 1 group/fixed | Healthy (18) | 10 ng/kg/min (15-20 min) | 23 (28%)  | 22 (19%) | 24 (35%)  |
| Magrini 1992 | 1 group, crossover/fixed  | Mild eHTN (8) | 3 ng/kg/min (15 min) rest | 1 (<1%) | 5 (3%) | 12 (12%) |
|  |  |  | 3 ng/kg/min (15 min) exercise | 1 (1%) | 1 (1%) | −1 (−1%) |
|  |  |  | 13 ng/kg/min (15 min) rest | 17 (15%) | 22 (14%) | 18 (18%) |
|  |  |  | 13 ng/kg/min (15 min) exercise | 11 (8%) | 10 (5%) | 12 (11%) |
| Matsuda 1990 | 1 group/target | Diagnostic cardiac catheterization (17)(3 atypical chest pain, 14 remote MI) | 0.5-4.0 µg/min | -- | 35 (26%)g | -- |
| Nolan 1967 | Multiple protocols | Total (39) including: Normal CV (5) | 8 ng/kg/min (30-90 min) | 18 (18%) | -- | -- |
|  |  |  HTN (9) | 8 ng/kg/min (30-90 min) | 24 (19%) | -- | - |
|  |  |  RHD/CAD (7) | 10 ng/kg/min (30-90 min) | 20 (19%) | -- | -- |
|  |  |  Normal CV (6) | 28 ng/kg/min (30-90 min) | 23 (29%) | -- | -- |
| Palmgren 2003 | 2 groups/ incremental | Normotensive (10) | 0.1 ng/kg/min (30 min) | -- | 1 (1%) | 2 (3%) |
|  |  |  | 0.5 ng/kg/min (30 min) | -- | 5 (4%) | 7 (9%) |
|  |  |  | 1.0 ng/kg/min (30 min) | -- | 8 (6%) | 10 (13%) |
|  |  | Normotensive family history HTN (13) | 0.1 ng/kg/min (30 min) | -- | 3 (2%) | 2 (3%) |
|  |  |  | 0.5 ng/kg/min (30 min) | -- | 6 (5%) | 8 (10%) |
|  |  |  | 1.0 ng/kg/min (30 min) | -- | 12 (10%) | 10 (13%) |
| Radice 1975 | 2 group/fixed | Normal (15) | 75 ng/kg/min (max at 15 sec) | -- | 35 (28%) | 28 (35%) |
|  |  | Angina pectoris (14) | 75 ng/kg bolus (at 15 sec) | -- | 32 (26%) | 25 (31%) |
| Ramin 1994 | 1 group/incremental, target | Pregnant undergoing C-section with spinal anesthesia (10) | PD10 (15-20 min)Max allowed 33 ng/kg/min | 10 (13%) | -- | -- |
| Ronan 1975 | 2 groups/incremental, target range | Suspected CAD but normal arteriogram (7) | 2.7 ng/kg/min (4-5 min)range 1-6 ng/kg/min | 34 (--) | 33 (27%) | 19 (26%) |
|  |  | Chest pain, CAD (8) | 1.5 ng/kg/min (4-5 min)range 0.67-3 ng/kg/min  | 38 (--) | 40 (30%) | 21 (30%) |
| Saxena 2010 | 2 groups, 2 diets/fixedh | Postpartum women (≥8 mo) | 3 ng/kg/min (45 min) |  |  |  |
|  |  |  Normotensive pregnancy (15) |  High Nadiet | -- | 10 (10%) | -- |
|  |  |  |  Low Nadiet | -- | 2 (2%) | 6 (10%) |
|  |  |  Hypertensive pregnancy (10) |  High Nadiet | -- | 11 (10%) | -- |
|  |  |  |  Low Nadiet | -- | 10 (9%) | 8 (12%) |
| Schachinger 2004 | 2 groups/fixed | Normotensive, no history (15) | 1 ng/kg/min following acute or chronic ACE inhibition | 9 (--) | -- | -- |
|  |  | Normotensive, FH primary arterial hypertension (15) |  | 9 (--) | -- | -- |
| Schachinger 2006 | 1 group/target | Healthy (6) | 8.8 ng/kg (bolus) | 15 (--) | -- | -- |
| Schlaich 2002 | 1 group/incremental | Normotensive no FH (60) | 0.5 ng/kg/min (30 min) | 4.6 (5%) | -- | -- |
|  |  |  | 3 ng/kg/min (30 min) | 13.4 (15%) | -- | -- |
|  |  | Normotensive FH HTN (28) | 0.5 ng/kg/min (30 min) | 4.2 (5%) | -- | -- |
|  |  |  | 3 ng/kg/min (30 min) | 14.4 (16%) | -- | -- |
| Shenker 1988 | 1 group/incremental | Normal (13) | 16 pmol/min (15 min) (after 4 and 8 pmol/min) | 23 (--) |  |  |
| Udhoji 1964 | 1 group/target | Hypotensive shock (6)i | Dose, duration not reported | 34 (70%) | 43 (69%) | 26 (62%) |
| Uza 1973 | 2 groups/target | Hypertensive not overweight (10) | 6.6 ng/kg/min (90 min)(range 4.4-9.2 ng/kg/min) | -- | 27.5 (16%) | 20 (20%) |
|  |  | Hypertensive and overweight (10) | 6.35 ng/kg/min (90 min)(range 4.3-14 ng/kg/min) | -- | 36 (23%) | 20.5 (21%) |
| Vincent 1985 | 1 group, 3 conditions/targetj  | Healthy normotensive (6) | PD20 two 3-h periods in same day19.6 ng/kg/min (12.6-28.4)17.2 ng/kg/min (4.9-27.9) | 20 mmHg |  |  |
| Wilkinson 2001 | 1 group/incremental | Healthy (8) | 1 ng/kg/min (15 min) | 5 (6%) |  |  |
|  |  |  | 3 ng/kg/min (15 min) | 15 (18%) |  |  |
|  |  |  | 6 ng/kg/min (15 min) | 21 (25%) |  |  |
|  |  |  | 10 ng/kg/min (15 min) | 30 (36%) |  |  |
| Yamamoto 1975 | 5 groups/fixed | Normotensive (5) | 10 ng/kg/min (30 min) | -- | -- | 19 (27%) |
|  |  | Conn's syndrome (5) |  | -- | -- | 29 (26%) |
|  |  | Renovascular HTN (4) |  | -- | -- | 18 (16%) |
|  |  | eHTN, low renin (11) |  | -- | -- | 25 (26%) |
|  |  | eHTN, normal/high renin (9) |  | -- | -- | 24 (26%) |

|  |
| --- |
| CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; eHTN, essential hypertension; ESRD, end-stage renal disease; FH, family history; HTN, hypertension/hypertensive; MI, myocardial infarction; Na, sodium; NE, norepinephrine; PD20, dose of angiotensin II required to increase pressure by 20 mmHg; RHD, rheumatic heart disease. Double dash: data was not reported or could not be calculated because baseline value was not reported.a Target, dose was adjusted to achieve a fixed pressor response (increase in SBP, DBP, or MAP); fixed dose, each subject in a group received the same dose; incremental, each subject received sequential incremental doses.b For pressor target studies, dose mean or range is presented as reported.c Difference in means or mean difference is presented as reported in each publication. Some values were calculated post hoc for this review. d One subject received 2 infusions (1.25 and 2.5 µg).e Another 6 subjects received angiotensin II 30 min after receiving norepinephrine for 30 min. Two of 15 subjects were normotensive but had inactive glomerulonephritis; treatment sequence for these 2 subjects was not identified.f Infusion included tritiated norepinephrine tracer; specific activity was not reported.g Left ventricular peak systolic pressure.h Angiotensin infusion on 7th day of high or low sodium diet. Three subjects in the hypertensive pregnancy group completed the high sodium diet period of the study but withdrew before completing the low sodium diet period.i A total of 12 patients received angiotensin II, but data suitable for this table were available for 6 patients.j On 3 separate days, subjects received increasing doses of angiotensin II with placebo, IV trimazosin, or oral trimazosin to compare PD20 values (the dose of angiotensin required to raise MAP by 20 mmHg).**Notes:** Full reference citations are provided in **Supplemental Content 1**. |