Vascular Effects of Ovarian Hormones

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Epidemiological background

- Stampfer et al *Prev Med 1991 20:47-63*
  - 5 hospital based cohort studies
  - 6 population based case control studies
  - 3 cross sectional angiographic studies
- Of 16 prospective studies 15 showed ⇓ mortality
  - overall a 56% relative risk for current users of ERT
- *Not entirely attributable to known lipid effects*

Direct infusions

- Local infusion into uterine artery (3mcg)
  - 2 hours later $\Rightarrow$ 600% $\Uparrow$ uterine blood flow
  - no change in cardiac output or BP
- Intravenous infusion (1mcg/kg)
  - 2 hours later $\Rightarrow$ 26% $\Uparrow$ cardiac output
  - Mean BP unchanged

Magness et al *Am J Physiol 1989 256:E536-542*

Coronary vasculature

- 3μM oestradiol ⇒ 82% relaxation of contracted coronary rings
  - within 5 minutes, maximal within 40 minutes
  - independent of endothelium
- Relaxation in arteries from women > men

Mugge et al *Cardiovasc Res 1993 27:1939-42*

- *Rapid effect, gender difference*

Coronary ischaemia - acute

- 11 postmenopausal women with coronary disease undergoing treadmill exercise testing
- Sublingual oestrogen
  - increased time to chest pain
  - increased time to ischaemic ECG changes

Rosano et al *Lancet 1993 342:133-6*

- *?mechanism, ?calcium blockade, ?nitric oxide ?haemodynamic, ?vasodilatation*

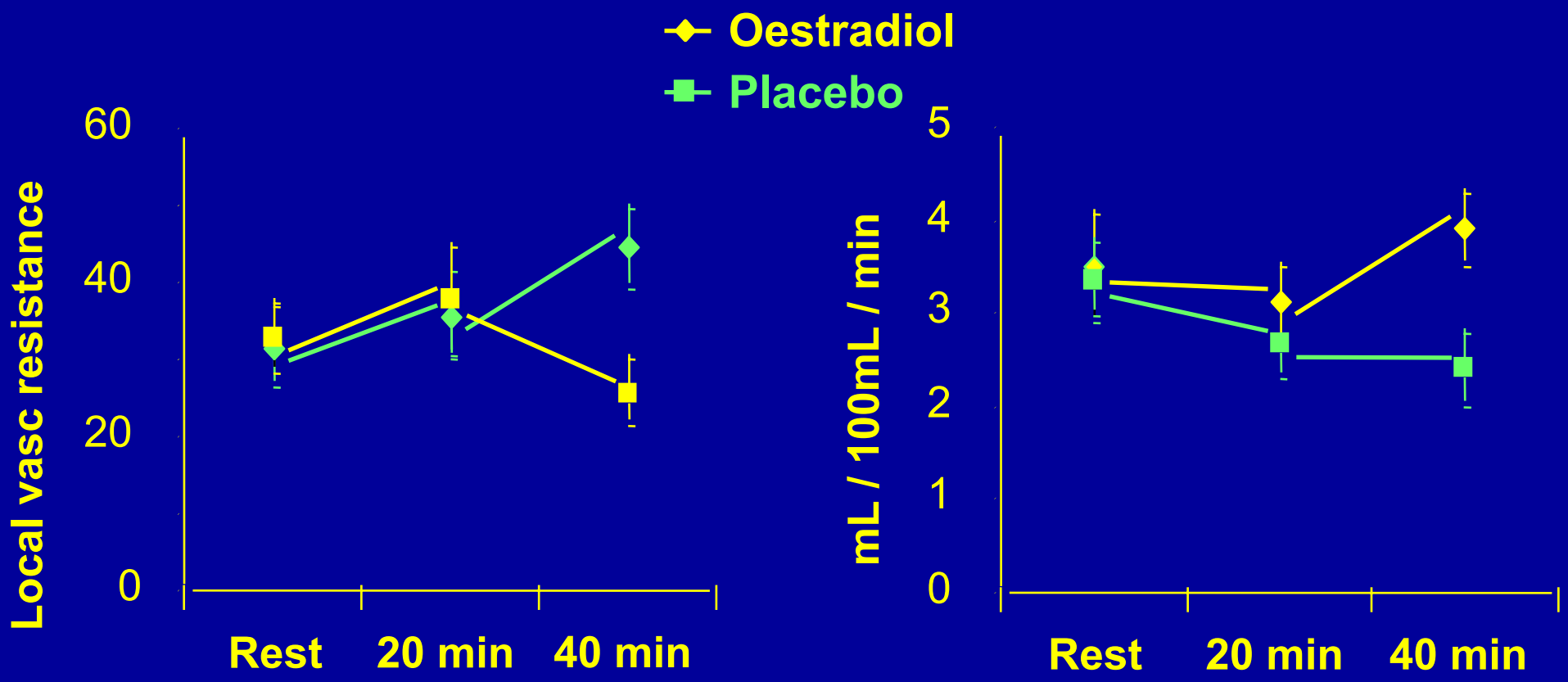
Forearm blood flow - acute

- Forearm studies using strain gauge plethysmography
  - Sublingual oestrogen
  - No change in blood flow after 20minutes
  - Significant increase after 40minutes

  Volterrani et al *Am J Med 1995 99:119-22*

- *Rapid effects on blood flow*

Forearm blood flow - acute



Volterrani et al *Am J Med 1995 99:119-22*

Coronary artery flow - acute

- Coronary flow studies in postmenopausal women undergoing angiography
- Acute oestrogen (IV Ethinyl estradiol, IC estradiol)
  - blocked vasoconstriction to acetyl choline
  - increased coronary flow (to IV EE)

    Reis et al *Circulation 1994 89:52-60*

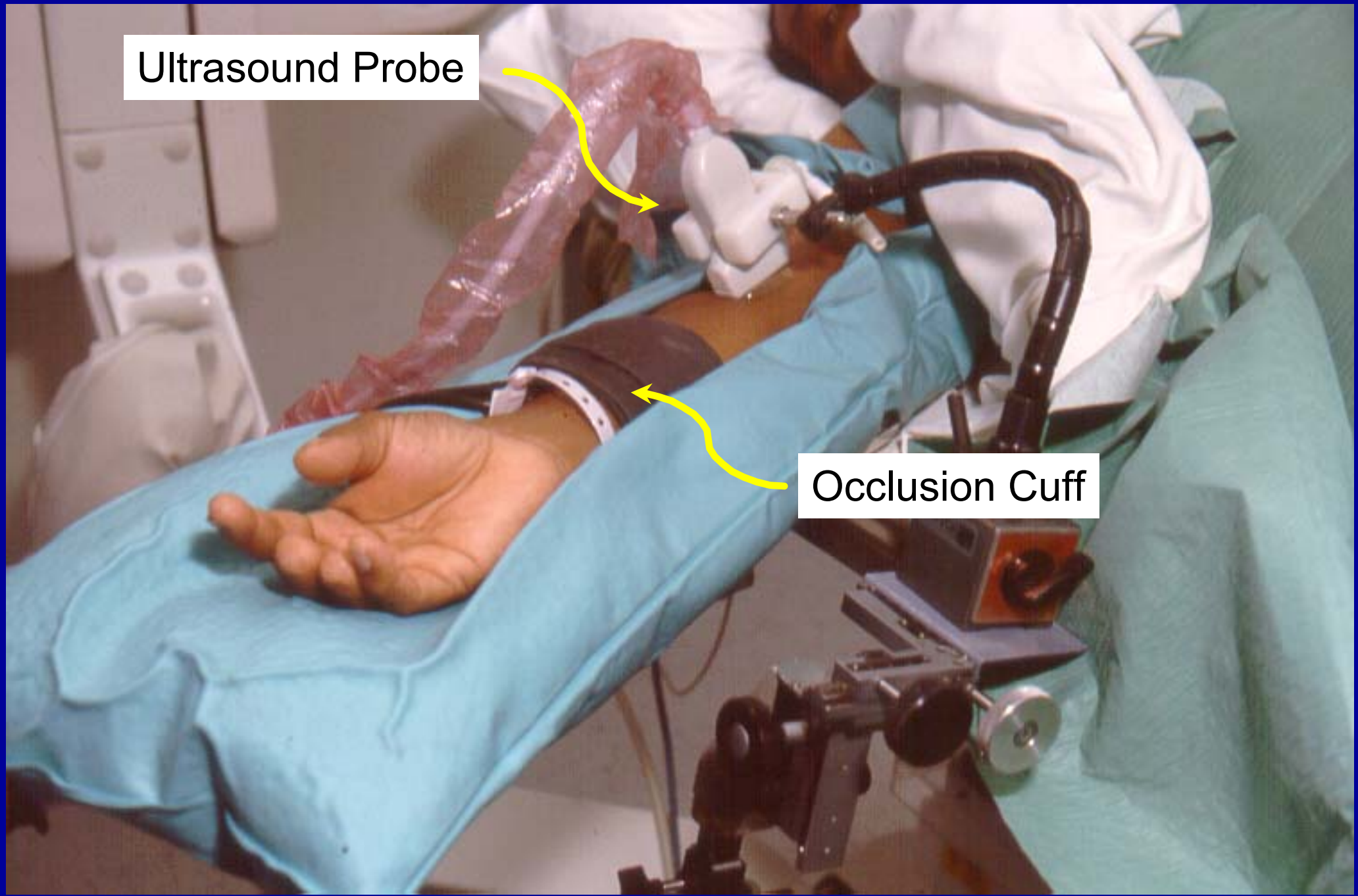
    Gilligan et al *Circulation 1994 89:2545-51*
- *Rapid, endothelium related action*

Brachial artery flow - HRT

- Brachial artery studies can be performed non-invasively, repetitively in healthy subjects.
- 9 weeks oestradiol 1mg, 2mg
  - improved flow mediated brachial artery dilatation
  - no effect on dilatation due to nitroglycerin

  Lieberman et al *Ann Intern Med 1994 121:936-41*
- 12 weeks HRT (oestradiol ± progesterone)
  - improved flow mediated dilatation
  - no adverse effect of progesterone

  Gerhard et al *Circulation 1998 98:1158-63*


Ultrasound Probe
Occlusion Cuff

Coronary ischaemia - acute

- Rapid pacing to induce ischaemia in postmenopausal women undergoing angiography
- Acute oestrogen (SL oestradiol)
  - decreased ischaemia (assessed by coronary sinus pH)
  - increased time to ischaemia

  Rosano et al *Circulation 1997 96:2837-41*
- *Not dependent on preconditioning*

Arterial physiology - Normal hormonal variation

- Healthy menstruating women, measurements during normal menstrual cycle
  - Brachial flow mediated dilatation greater during follicular & luteal phases
  - Similar to males in menstrual phase

    Hashimoto et al *Circulation 1995 92:3431-5*
  - Radial artery distensibility increased during ovulatory phase and decreased during luteal phase

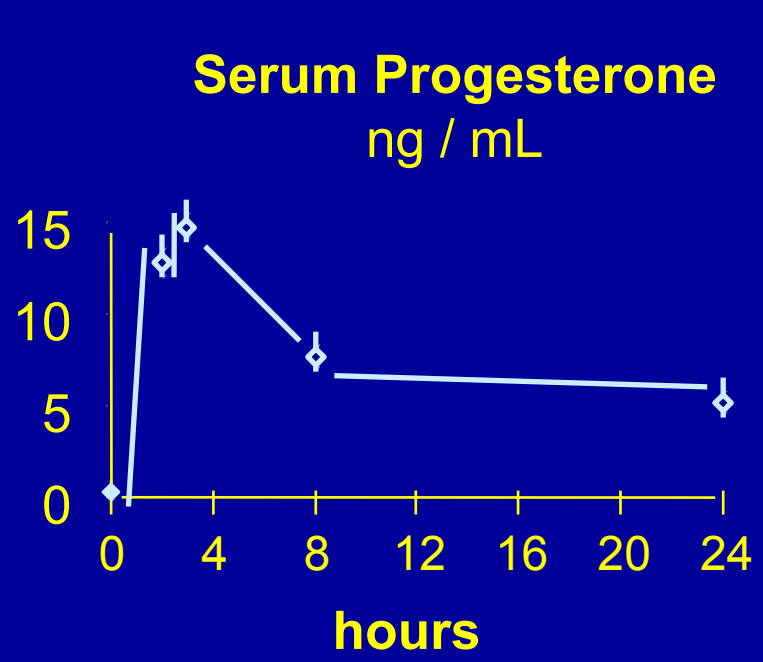
    Giannattasio *Arterioscler Thromb Vasc Biol 1999 19:1925-9*

Progesterone flow effects

- 12 healthy postmenopausal women
- Forearm plethysmography
- Acute progesterone (vaginal cream)
  - decreased baseline flow
  - increased resistance

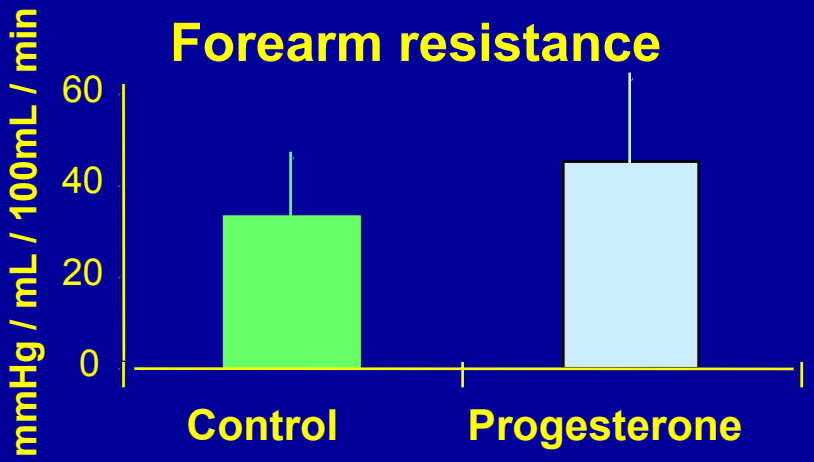
Mercuro et al *Am J Cardiol 1999 84:214-8*

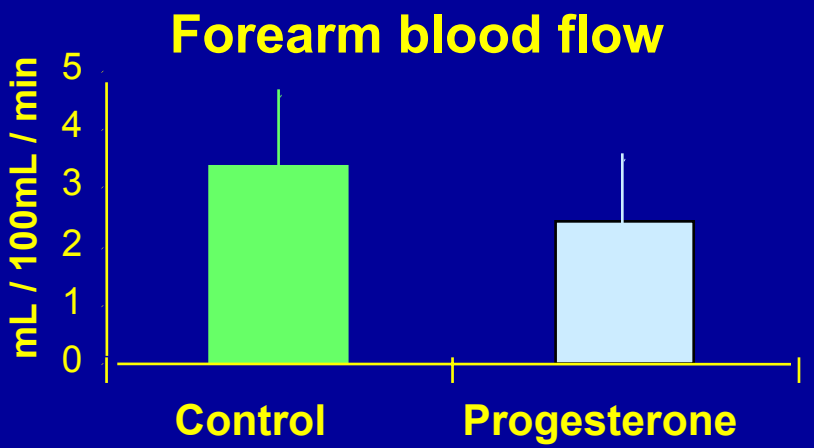
Progesterone flow effects



Blood flow measurements at 3 hours

Mercuro et al *Am J Cardiol 1999 84:214-8*





Flow summary

- Oestrogen increases blood flow directly
- Related to an intact endothelium
- Specific to 17β oestradiol rather than 17α oestradiol
- Cyclical variations seen in line with menstrual cycle
- *Does not explain cardiovascular protection*

Oestrogen Receptor α

- Oestrogen and progesterone receptors had been identified in the vasculature in animals previously
- Post-mortem study in 40 women - E2R detected on VSMC, mainly on those without coronary disease

Losordo et al *Circulation 1994 89:1501-10*

- Internal mammary Aa and saphenous Vv

Karas et al *Circulation 1994 89:1943-50*

Oestrogen Receptor Isoforms

- Receptor isoform demonstrated in VSMC from internal mammary artery and saphenous veins
  - Widely distributed throughout the cell (not just nuclear)

    Karas et al *FEBS Lett 1995 377:103-8*
- 5 additional isoforms described so far

  Hodges et al *Circulation 1999 99:2688-93*
- Chronic vascular effects most likely receptor mediated

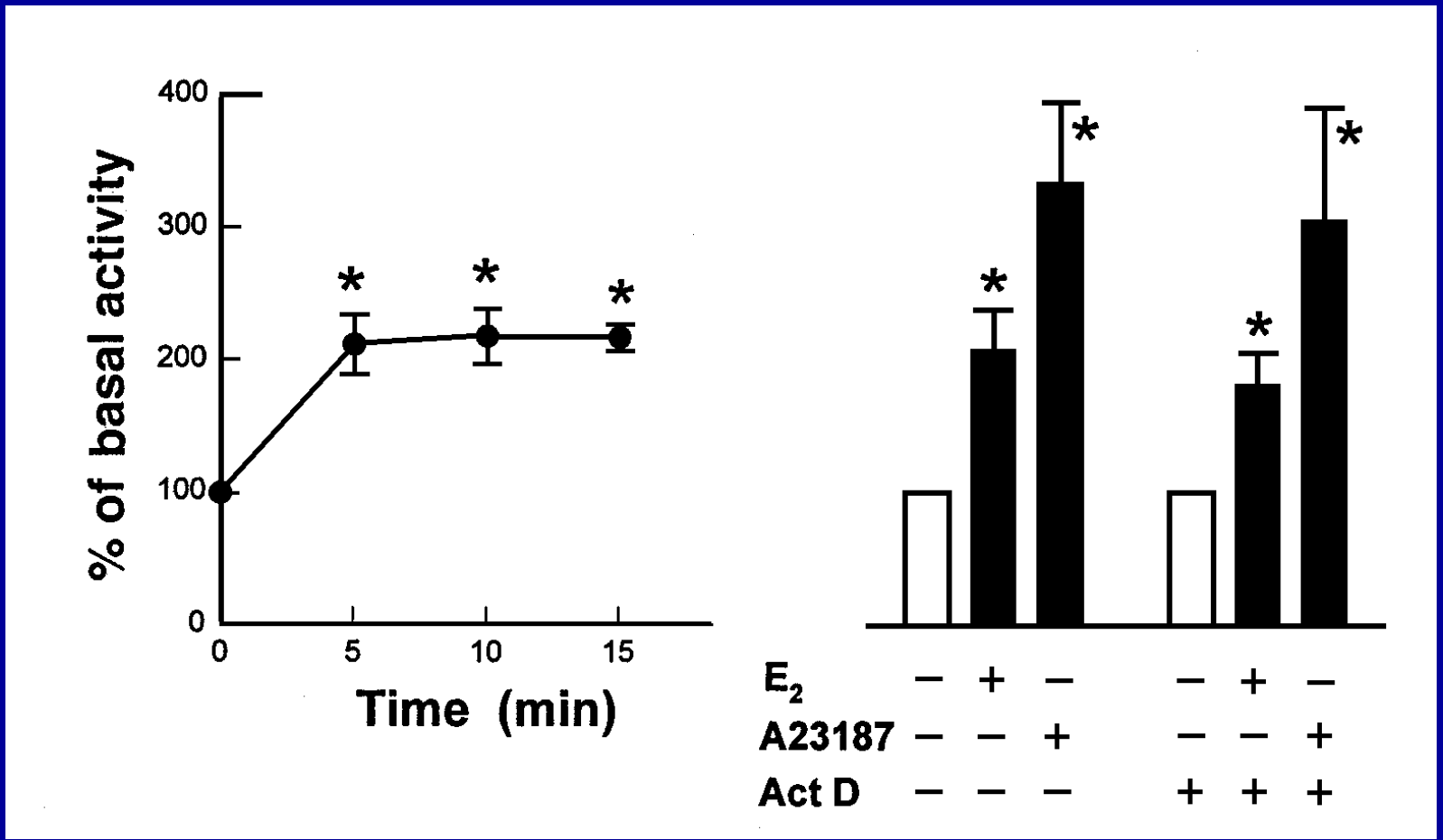
Rapid, yet receptor mediated

- Increases seen in blood flow occur within 5 minutes
- Blocked by oestrogen receptor antagonists
- Associated with increased nitric oxide production
- *?mechanism*
- eNOS ⇑ by MAP kinase activation independent of gene transcription

  Chen et al *J Clin Invest 1999 103:401-6*
- Surface oestrogen receptor in caveolae

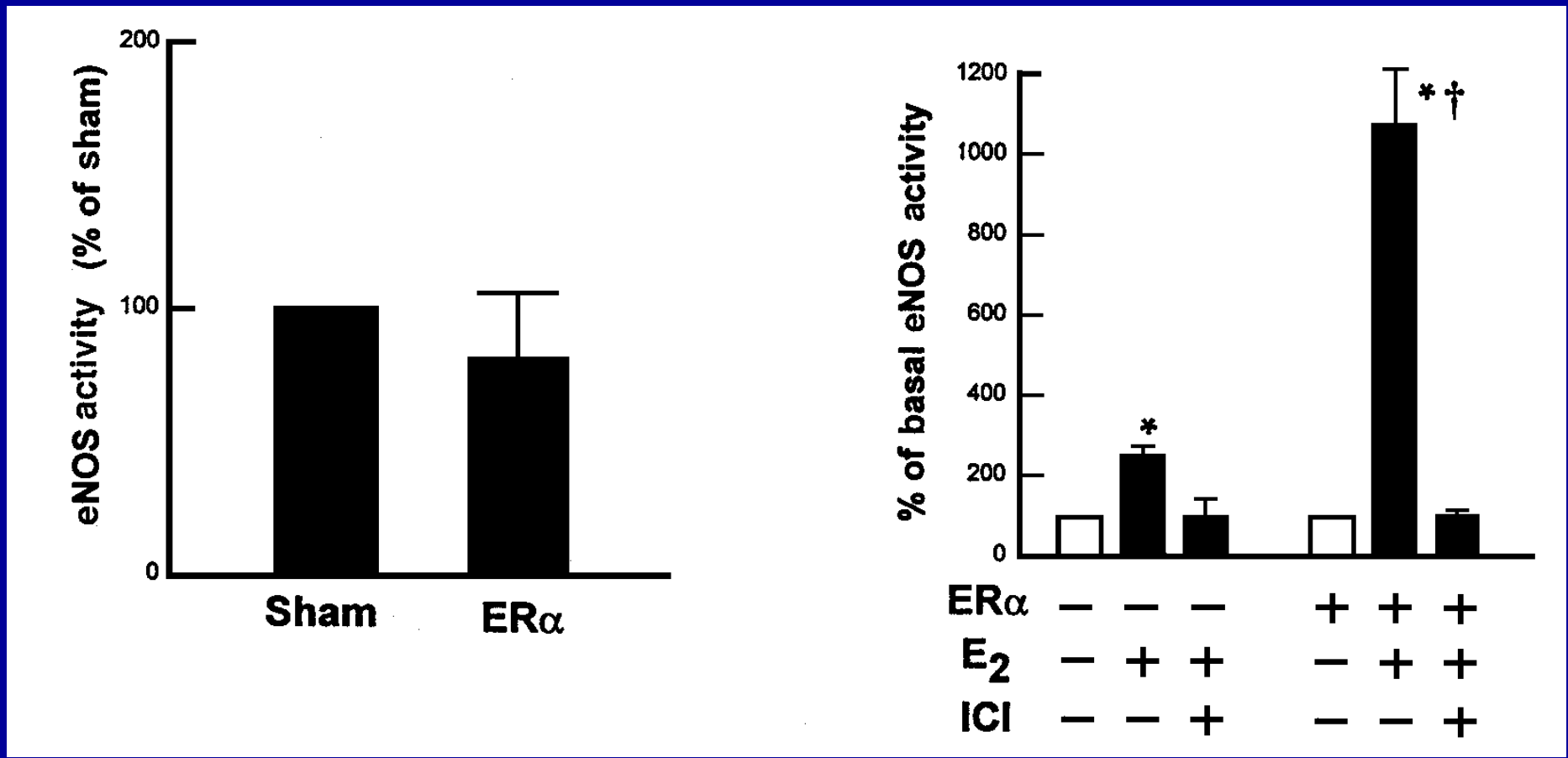
  Kim et al *Biochem Biophys Res Commun 1999 263:257-62*

Rapid eNOS activation, non genomic



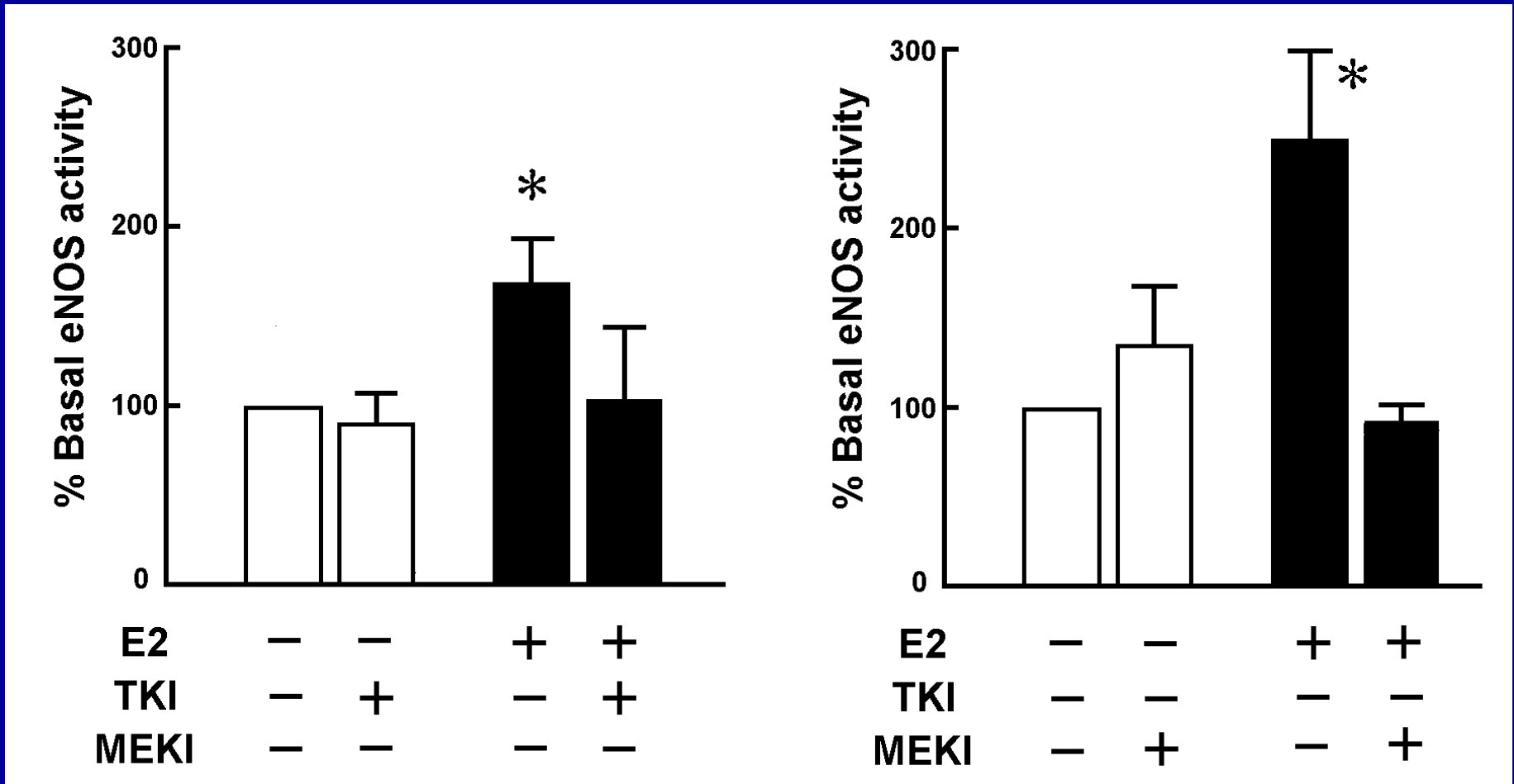
Chen et al *J Clin Invest 1999 103:401-6*

E2α (classic) receptor mediated



Chen et al *J Clin Invest 1999 103:401-6*

MAP kinase dependent

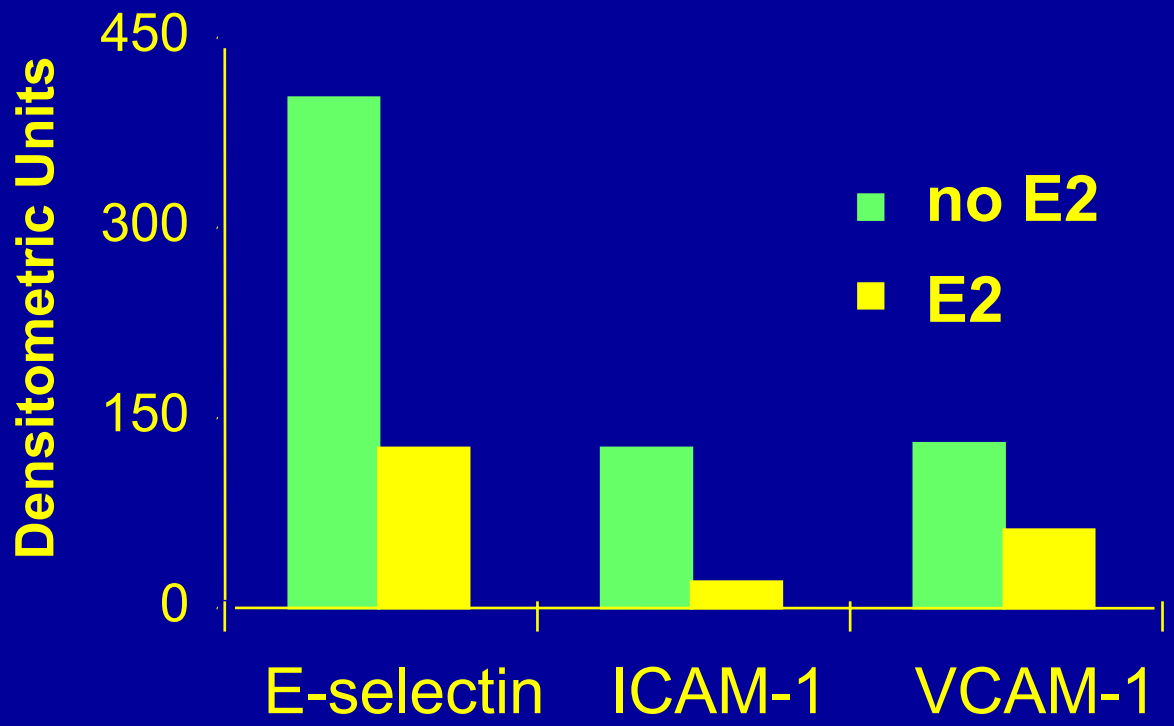


Chen et al *J Clin Invest 1999 103:401-6*

Atherogenic protection by E2 - Endothelium

- E2 decreases cellular adhesion molecules
  - IL-1 mediated E-selectin, vCAM-1, iCAM-1 expression
  - 17αE2 has no effect Caulin-Glaser *J Clin Invest 1996 98:36-42*
- E2 increases endothelial cell junction tightness - concentration dependent Cho *Am J Physiol 1999 276:C337-49*
- E2 inhibits endothelial apoptosis Alvarez *BBRC1997 237:372-81*

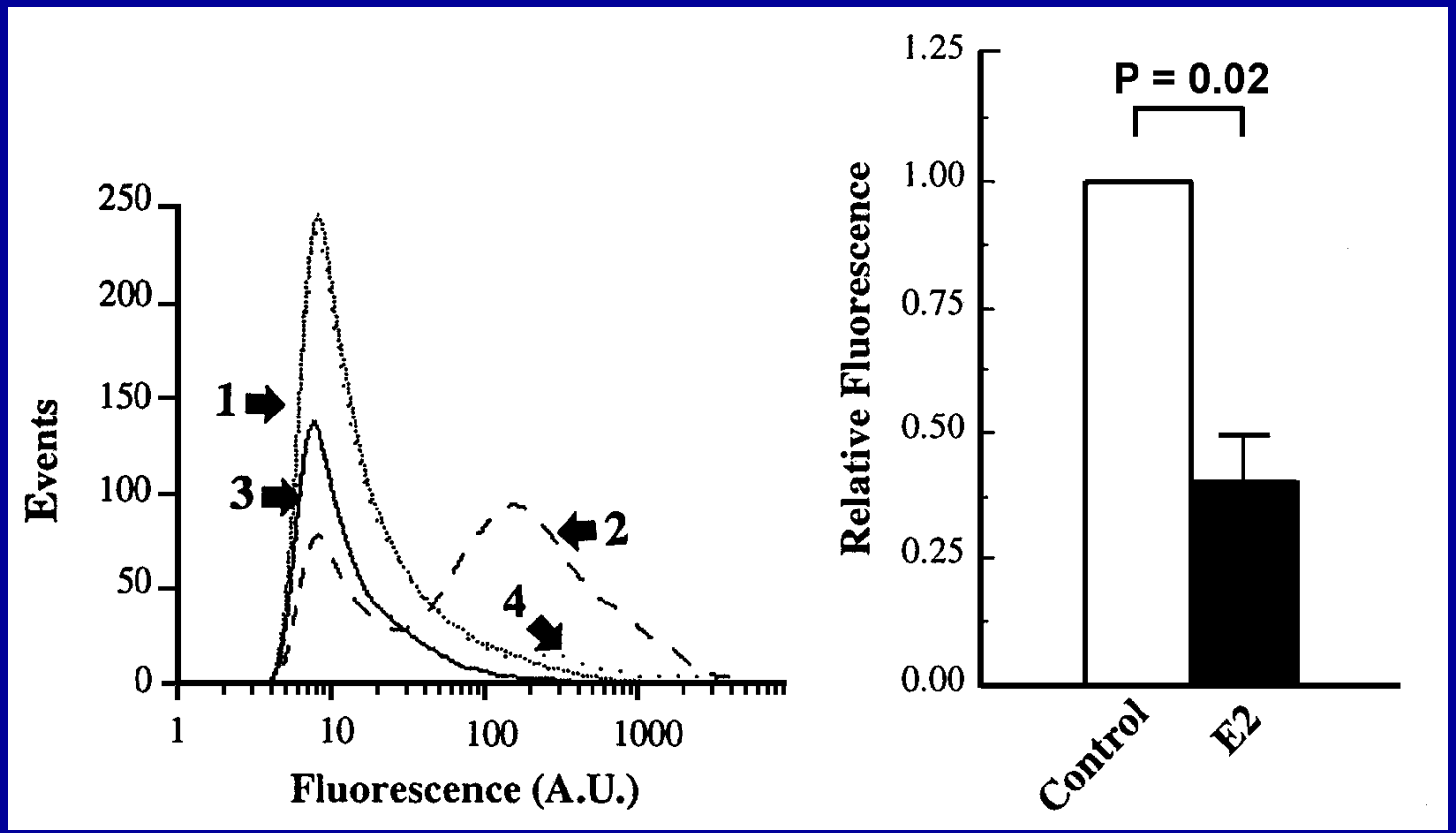
E2 decreases cellular adhesion molecules



- HUVEC propagated + / - E2
- Activated by IL-1 for 1.5 hours
- Nuclear transcripts

Caulin-Glaser et al *J Clin Invest 1996 98:36-42*

E2 decreases endothelial cell apoptosis



- Bovine Aortic EC propagated + / - E2 (10^{-8}M)
- Apoptotic cells stained with Fluorescein-TUNEL assay

1 E2+ **2** E2- **3** E2 medium **4** Low E2 medium

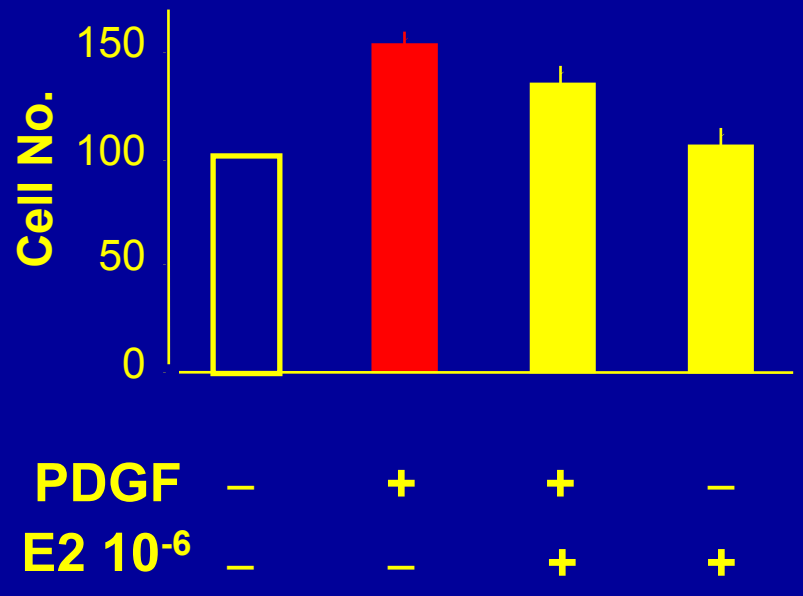
Alvarez et al BBRC 1997 237:372-81

Arterial wall remodelling by E2

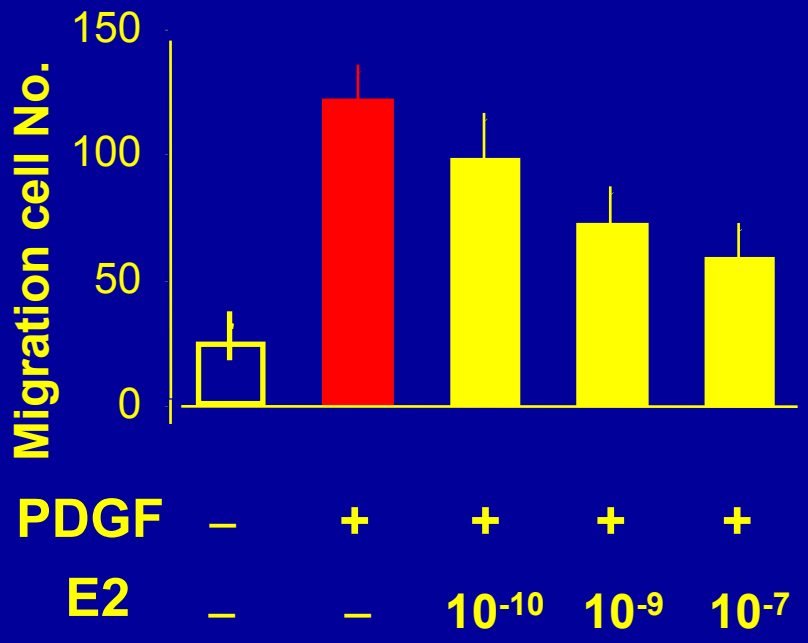
- E2 beneficial remodelling effects
  - decreases smooth muscle cell proliferation, migration *in vitro*
    Dai-Do *Cardiovasc Res 1996*
  - decreases arterial wall cholesterol incorporation
  - decreases collagen content *in vivo* Register *ATVB 1998*
- HRT no effects on carotid wall thickness - ARIC, n=2385 women Nabulsi *Circulation 1996*
- HRT withdrawal ⇑ arterial stiffness Waddell *J Hypertens 1999*

E2 decreases VSMC proliferation, migration

VSMC from postmenopausal women
10 days of stimulation

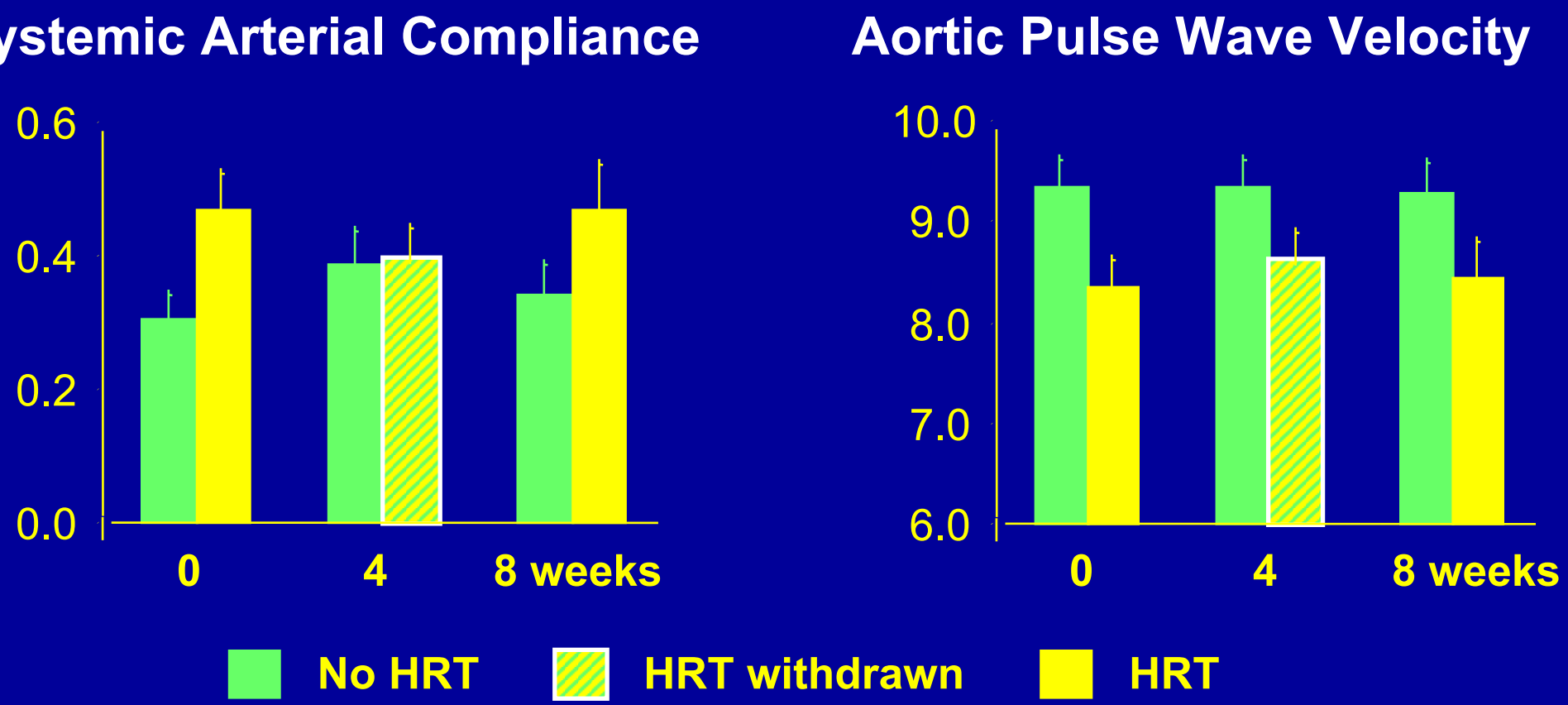


Human VSMC
48 hours of culture
24 hours of E2 + / -



Dai-Do et al *Cardiovasc Res 1996 32:980-5*

HRT withdrawal increases arterial stiffness



Waddell et al *J Hypertens 1999 17:413-8*

Progesterone effects

- FMD improved by both E2 and E2+P Gerhard *Circulation 1998*
- Combined HRT no effect on FMD Sorensen *Circulation 1998*

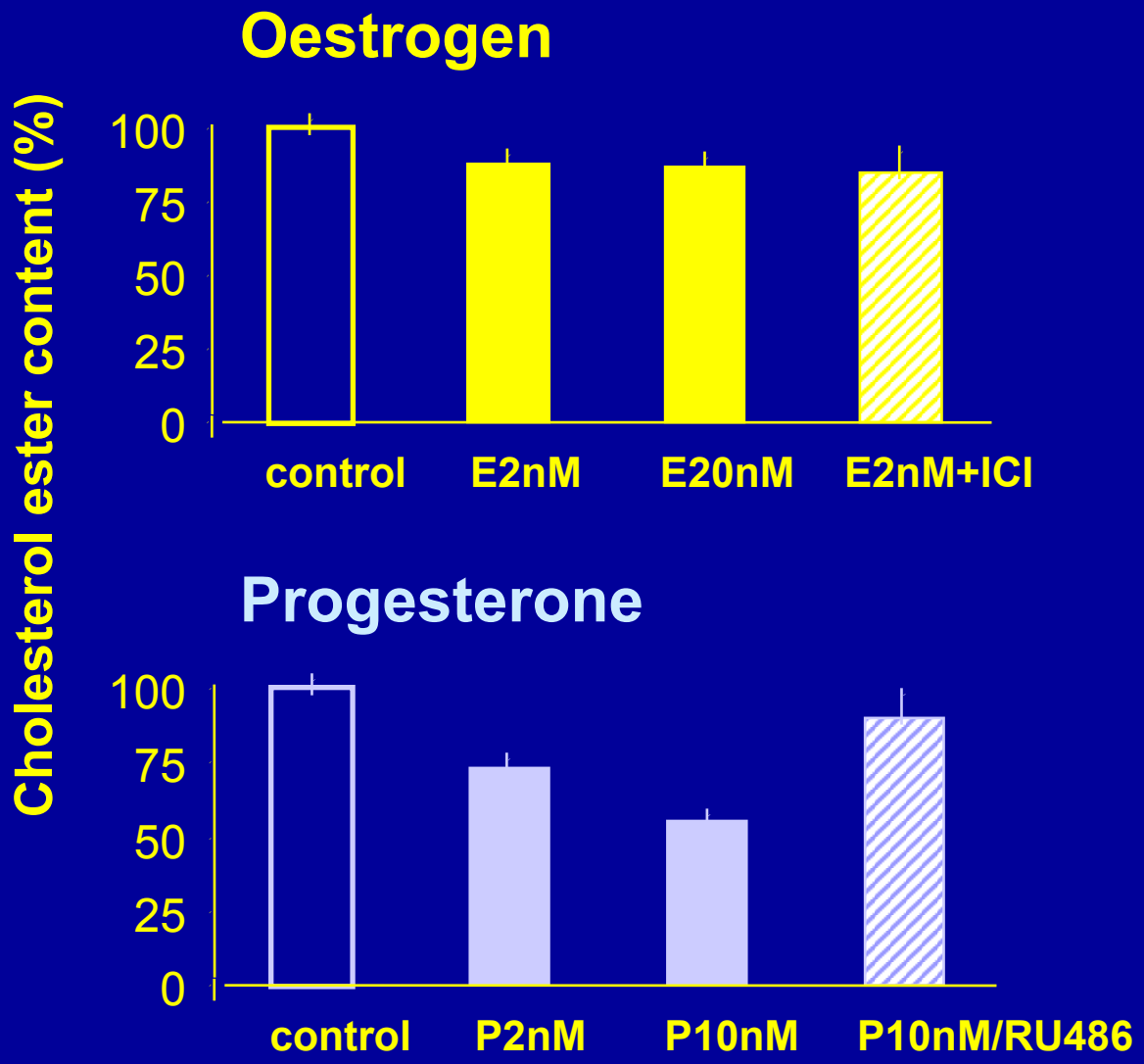
- E2 and P inhibit VMSC proliferation Morey *Endocrinology 1997*
- E2 but not P inhibit hAoVSMC proliferation, E2+P not affected Suzuki *Cardiovasc Res 1996*

Progestins - Summary

- Progestagens have different metabolic effects
- They also differ in their vascular activity
  - Vascular dilatation
  - Cellular proliferation

- Natural progesterone most beneficial
- MPA has least beneficial profile

Foam cell formation



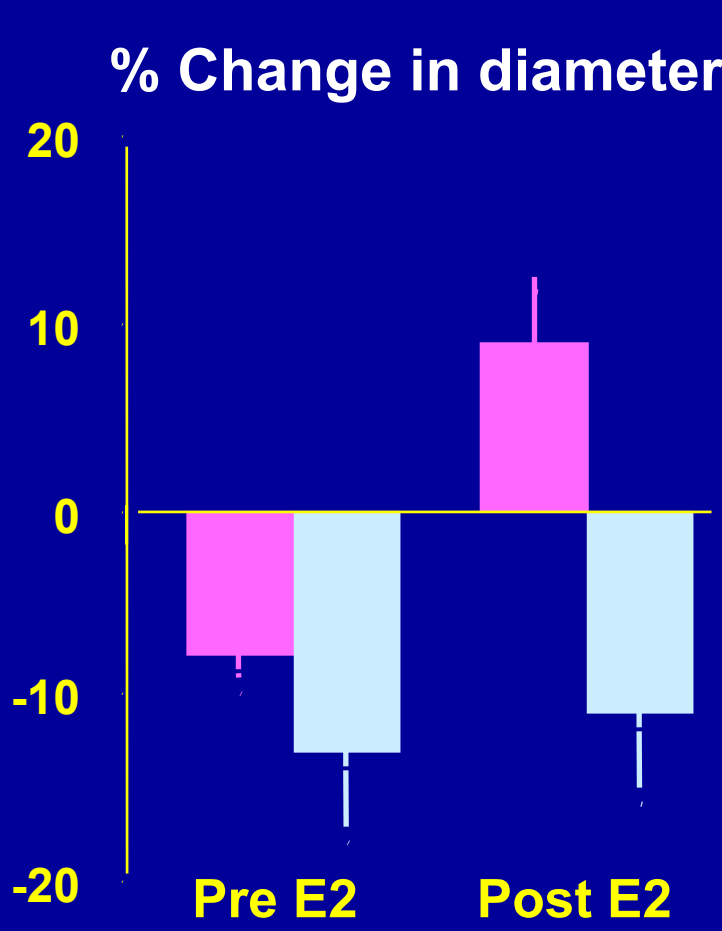
- E2 significant decrease in CE content
- Receptor independent
- P greater inhibition of CE accumulation
- Receptor dependent
- Sex specific

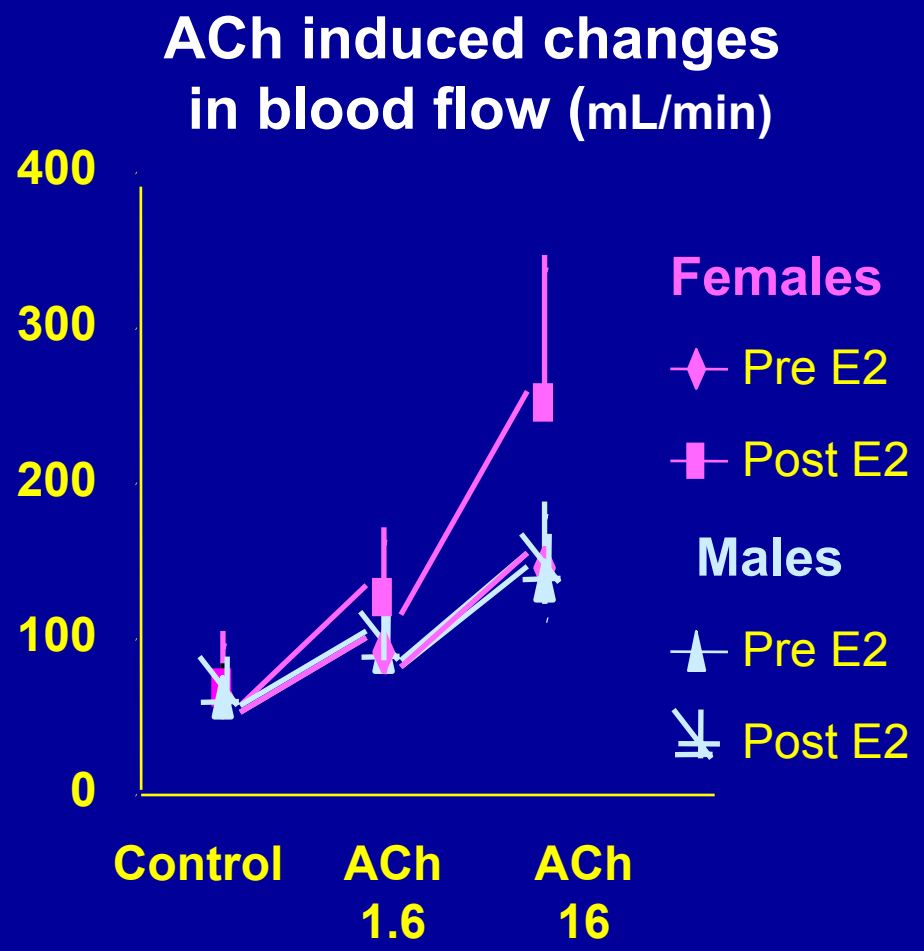
McCrohon *Circulation 1999 100:2319-25*

Gender issues

- Oestrogen does not act acutely in men
  - Coronary flow studies
  - Brachial flow studies
- Long term oestrogen does increase brachial flow in transsexual populations
- E2, P no effect on cholesterol incorporation in male macrophages
- E2, P similarly effective in men and women in inhibition of VSMC proliferation, migration

E2, Gender coronary effects





Collins *Circulation 1995 92:24-30*

Ongoing questions

- Role of progestins on vascular function
- Effect of different types of progestins
- Gender differences in responses to oestrogens
- Effect of androgens on vascular function in women
- SERM's and vascular function