An introduction to the somatic side effects of androgen abuse

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Overview

1. Erythrocytosis or polycythemia
2. Acne
3. Male-pattern hair loss (androgenetic alopecia)
4. Prostate growth and cancer
5. High blood pressure (hypertension)
6. Liver toxicity (hepatotoxicity)
7. Dyslipidemia
8. Kidney toxicity (nephrotoxicity)
9. Testosterone deficiency
10. Infertility
11. Gynecomastia
12. Cardiomyopathy

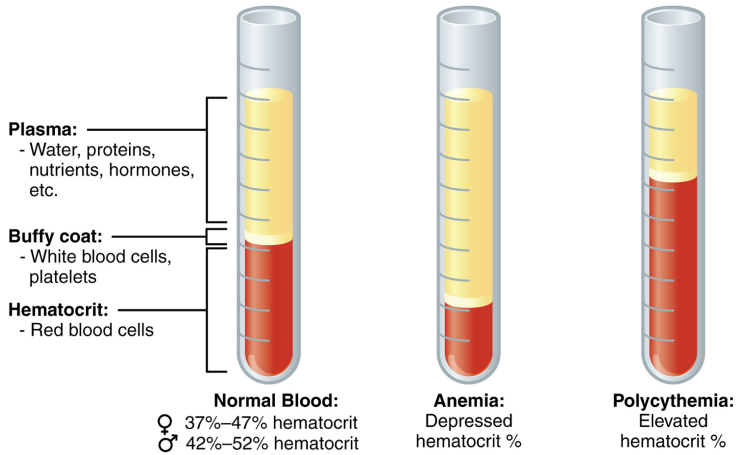
The HAARLEM study

Health risks of **A**nabolic **A**ndrogenic ste**R**oid use by ma**LE** a**M**ateur athletes

- Prospective observational cohort of 100 male amateur athletes using androgens
- Measurements before, at the end, and at two points in time after their cycles
- Median androgen dosage (based on label information) of 901 mg weekly
- Median cycle duration of 13 weeks

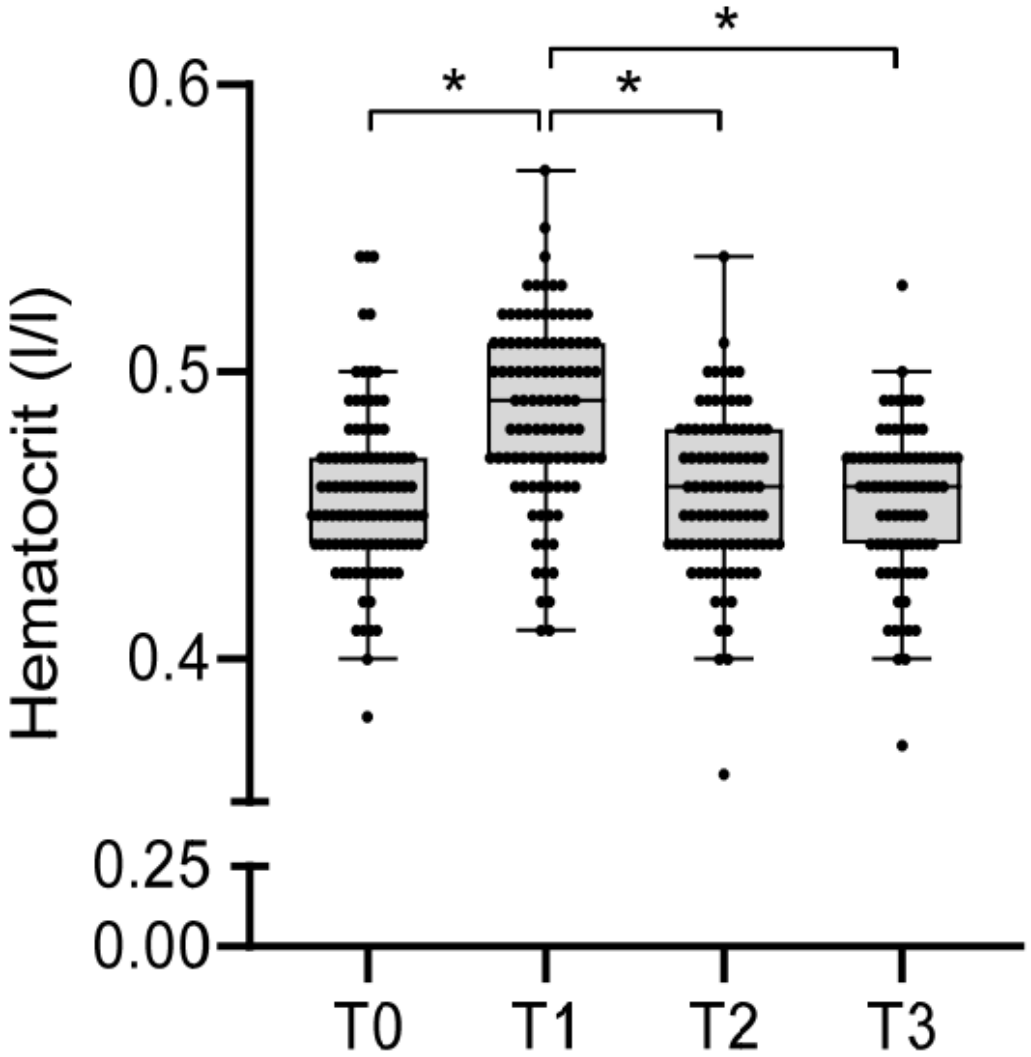
Erythrocytosis or polycythemia

- Erythrocytosis or polycythemia: an increase in blood hematocrit or hemoglobin levels
- It is a common side effect of androgen use (most common side effect on TRT!)
- Dose-dependent: higher doses lead to higher increases (but likely a 'ceiling effect' at roughly 500 mg weekly)
- Age-dependent: older men experience a larger increase than young men (8 %p and 4 %p, respectively, on 600 mg testosterone enanthate weekly)



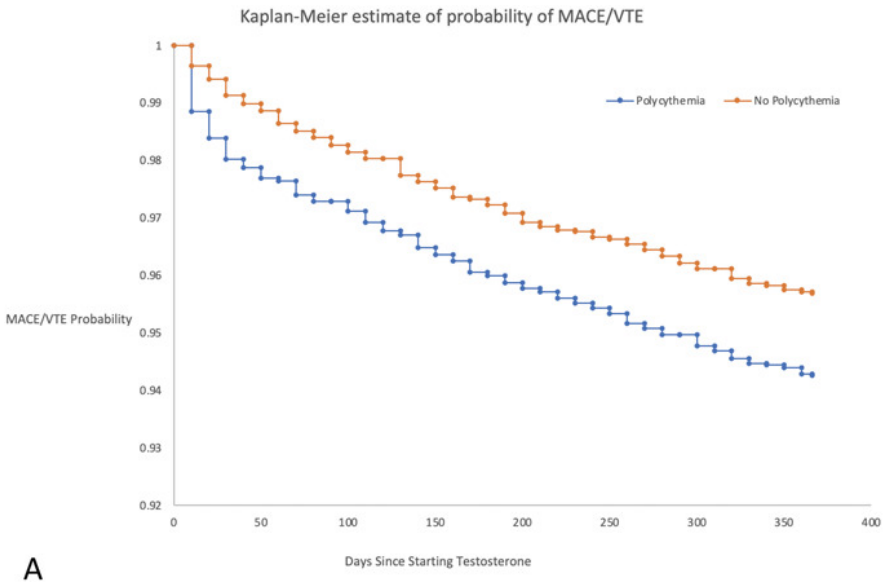
Erythrocytosis or polycythemia

HAARLEM study



Erythrocytosis or polycythemia

- Norwegian Tromsø study: 33 % higher chance of a venous thromboembolic event for every 5 %p increase in hematocrit (in men)
- Retrospective cohort study of testosterone-deficient men receiving TRT showed higher risk of MACE/VTE in those with hematocrit $\geq$52% compared with those $<$52%



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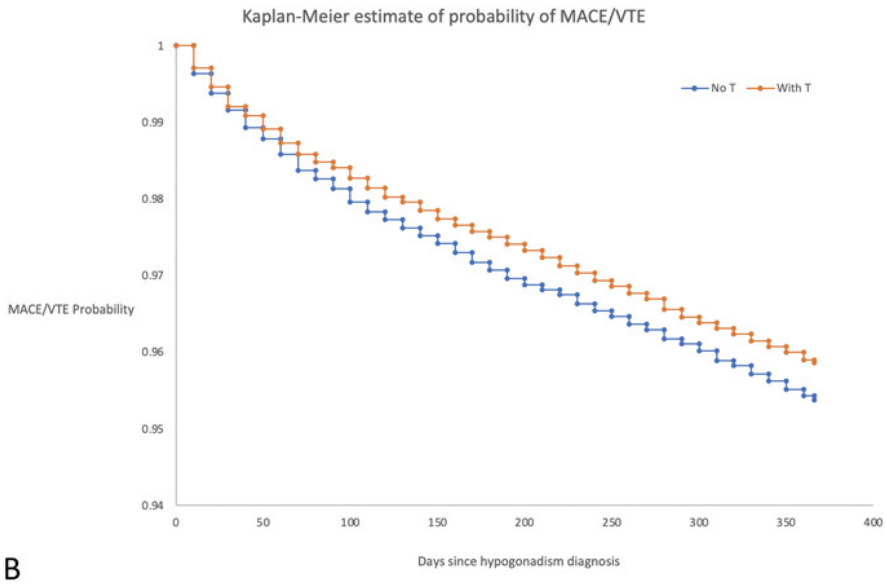

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Erythrocytosis or polycythemia

- Phlebotomy decreases hematocrit but unclear if it affects MACE/VTE incidence
- Low-dose aspirin (acetylsalicylic acid; 75–100 mg daily); decreases risk of thrombosis but increases bleeding risk (gastric ulcer). Net benefit likely only in those at high cardiovascular disease risk

Acne

- HAARLEM study: self-reported prevalence 10 % at start, 52 % at the end of the cycle. Physician-identified: 13 % at start, 29 % at the end of the cycle.
- 50, 125, 300 or 600 mg testosterone enanthate weekly showed no effect on sebum production
  - lack of statistical power might have obscured an effect (?)
  - forehead sebum production was related to testosterone dose (but not nose and back sebum production were not)
- Androgens might affect follicular keratinization
- Users self-treat with various supplements, but also (prescription) medications such as topical retinoids or isotretinoin (Roaccutane)
- While merely cosmetic, it can (heavily) impact quality of life and leave scars

Male-pattern hair loss (androgenetic alopecia)

- Androgen-dependent condition par excellence:
  - Castrated men do not develop male-pattern hair loss unless treated with testosterone
  - Men born with 5α-reductase deficiency do not develop male-pattern hair loss either
  - Pharmaceutical treatment targets 5α-reductase (Finasteride; a 5α-reductase inhibitor)
- Do high dosages of androgens accelerate or cause male-pattern hair loss?
- HAARLEM study: **self-reported** alopecia increased from 2 % at baseline to 12 % at the end of the cycle
- Self-medication with Finasteride on high dosages of androgens: unproven and dubious at best

Prostate growth and cancer

- Historically, effects on the prostate were a large matter of concern based on few case studies of testosterone treatment and animal experiments suggesting it caused prostate cancer
- The prostate serves as the 'model organ' for androgenic activity in the Hershberger assay
- MRI showed no change in prostate volume in healthy men receiving up to 600 mg testosterone enanthate weekly for 20 weeks
- Testosterone enanthate dosages up to 600 mg weekly did not affect serum prostate-specific antigen (PSA) levels in both healthy young and older men
- HAARLEM study: small increase in PSA levels (from 0.71 μg/L to 0.93 μg/L) of unknown importance (upper limit reference range: 2.0 μg/L)

Prostate growth and cancer

- Clinical data in the literature limited to 1 case report of prostate adenocarcinoma in a long-term androgen user
- 'Absence of evidence does not mean evidence of absence': trials to date not sufficiently powered and long enough in duration
- TRAVERSE study examines the relationship in TRT; large case-control studies of androgen users are required for more confidence with high dosages

High blood pressure (hypertension)

- HAARLEM study: increase of 7/3 mmHg in blood pressure. 41 % were hypertensive (>140/90 mmHg) during their cycle compared with 16 % at baseline
- Effect on cardiovascular disease risk hard to quantify, but:
  - Every 10 mmHg reduction in systolic blood pressure by pharmacological treatment reduces the risk of MACE, CHD, stroke, heart failure, and all-cause mortality by 20 %, 17 %, 27 %, 28 %, and 13 %, respectively
  - The inverse might hold true for a pharmacologically (androgen) induced increase
- Treatment by standard guidelines seems appropriate in long-term users, but no evidence for efficacy
- ACE inhibitors and ARBs are preferred as they do not affect exercise capacity (and are not prohibited by the WADA). Alternatively or additionally calcium channel blockers are a preferred choice in athletes

Liver toxicity (hepatotoxicity)

- Appears limited to orally bioavailable androgens that are 17α-alkylated (e.g. stanozolol, methandienone, oxandrolone, oxymetholone)
- Increases in biochemical markers of liver damage: ALT, AST, LDH, GGT, sometimes bilirubin
- Rarely clinical signs of liver damage, but might cause jaundice (yellowish pigmentation of the skin and eye whites) and pruritus (itching)
- Some case reports of peliosis hepatis, liver carcinoma and adenoma

Dyslipidemia

Type of androgen	LDL-C	HDL-C	CEC	Lp(a)
Injectable androgens	$\leftrightarrow$	$\downarrow$	$\downarrow\downarrow$	$\downarrow$
17α-alkylated androgens	$\uparrow\uparrow$	$\downarrow\downarrow$	$\downarrow\downarrow$	$\downarrow$

- Causal relationship between HDL-cholesterol and cardiovascular disease unclear
- Favorable effect on Lipoprotein(a) unlikely to negate the overall detrimental effect
- Might affect cholesterol efflux capacity (CEC)
- Users self-medicate with various supplements (e.g. red yeast rice extract, berberine, niacin) and/or statins

Kidney toxicity (nephrotoxicity)

- No good-quality evidence showing kidney damage
- Some findings suggestive of nephrotoxicity:
  - Small increases in serum creatinine (but pitfalls with interpretation)
  - Elevated cystatin C (one cross-sectional study)
  - HAARLEM study: albuminuria (measured with dipstick analysis) emerged or increased in 16 % of subjects
  - Reports in the literature of focal segmental glomerulosclerosis in (heavy) long-term androgen users

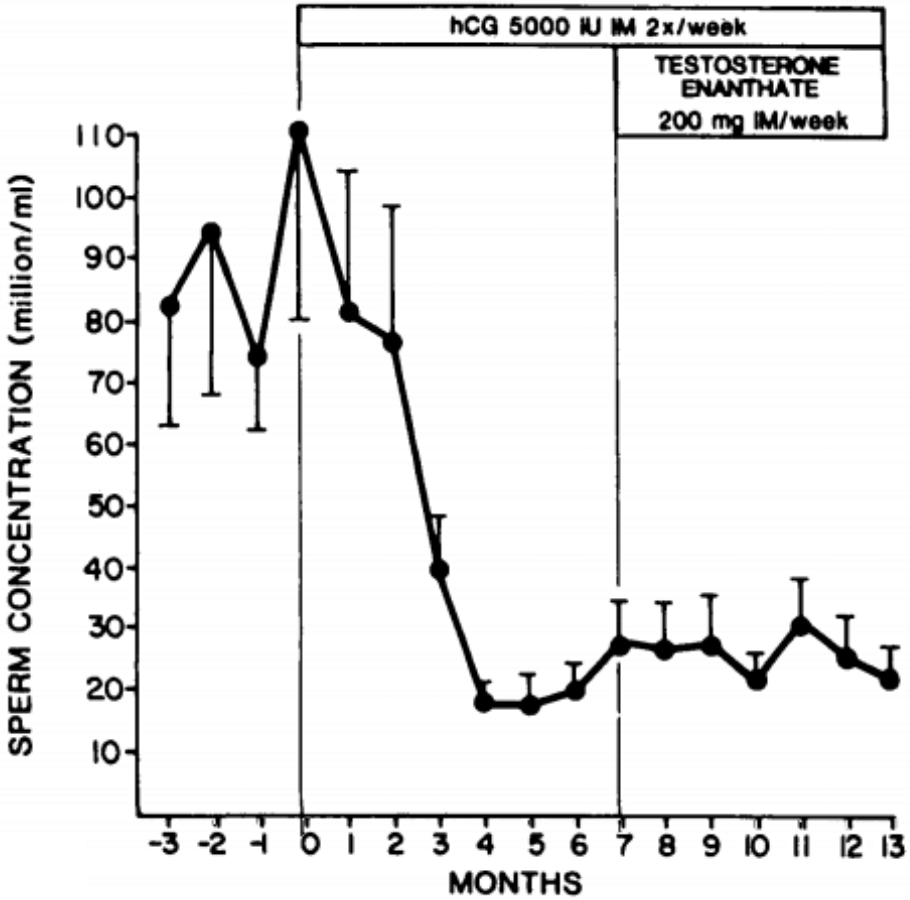
Testosterone deficiency

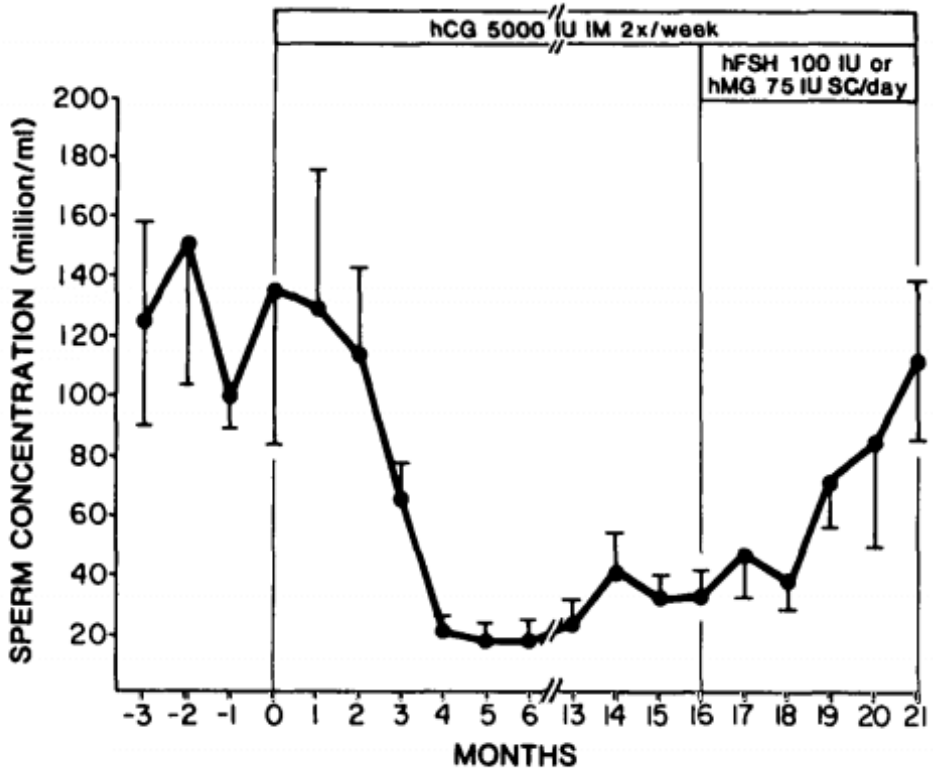
- Androgens and their estrogenic metabolites suppress testosterone production
- HAARLEM study: 90 % of users that had normal gonadal function at baseline recovered within 3 months after stopping androgen use (and 100 % at end of follow-up)
- 37 % had abnormal gonadal function at baseline, of which 95 % had a history of AAS use (caused by recent androgen use or permanent damage to endogenous production with long-term use?)
- Users self-medicate ('post-cycle therapy') with selective estrogen receptor modulators (SERMs) such as tamoxifen and clomiphene, aromatase inhibitors such as exemastane, letrozole and anstrozole, and human chorionic gonadotropin (hCG); but lack of evidence

Infertility

- Androgens and their estrogenic metabolites suppress sperm production
- HAARLEM study: two-thirds of subjects were azoo- or oligozoospermic at the end of their cycle
- Time course and extend of recovery from hormonal male contraceptive studies:
  - median time for sperm count recovery to baseline of 5.4 months
  - 54 % recovering within 6 months
  - 83 % recovering within 12 months
  - 95 % recovering within 16 months
  - 100 % recovering within 24 months
- Take-home: recovery is slow!
- Users self-medicate with human chorionic gonadotropin (hCG) and/or human menopausal gonadotropin (hMG)

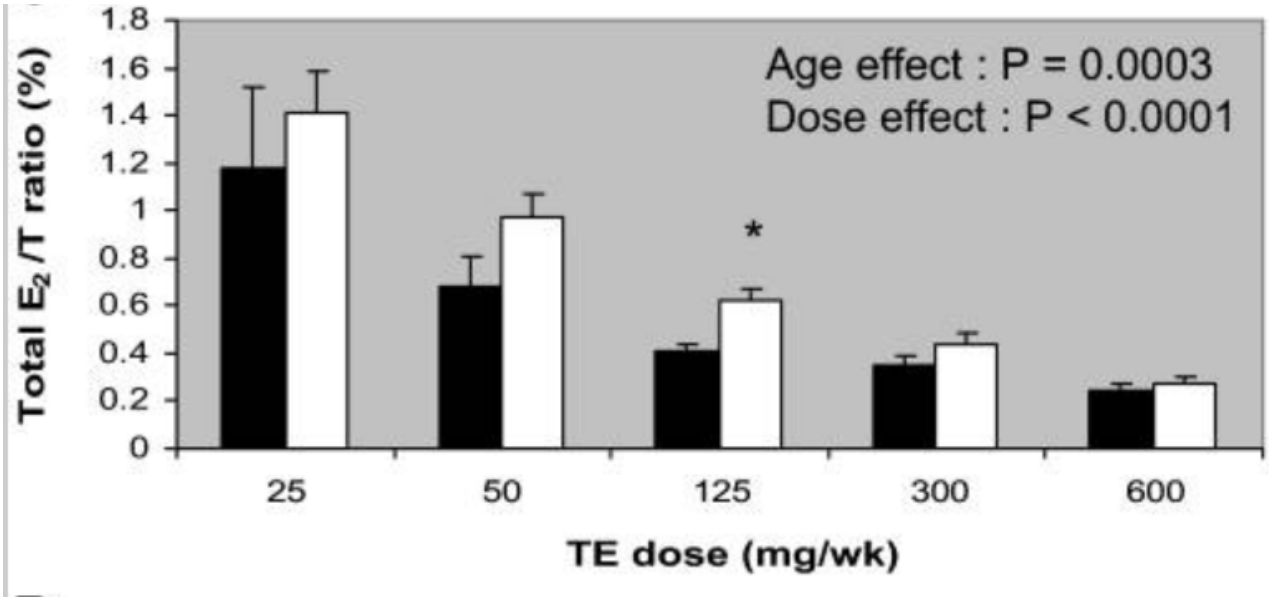
Infertility





Gynecomastia

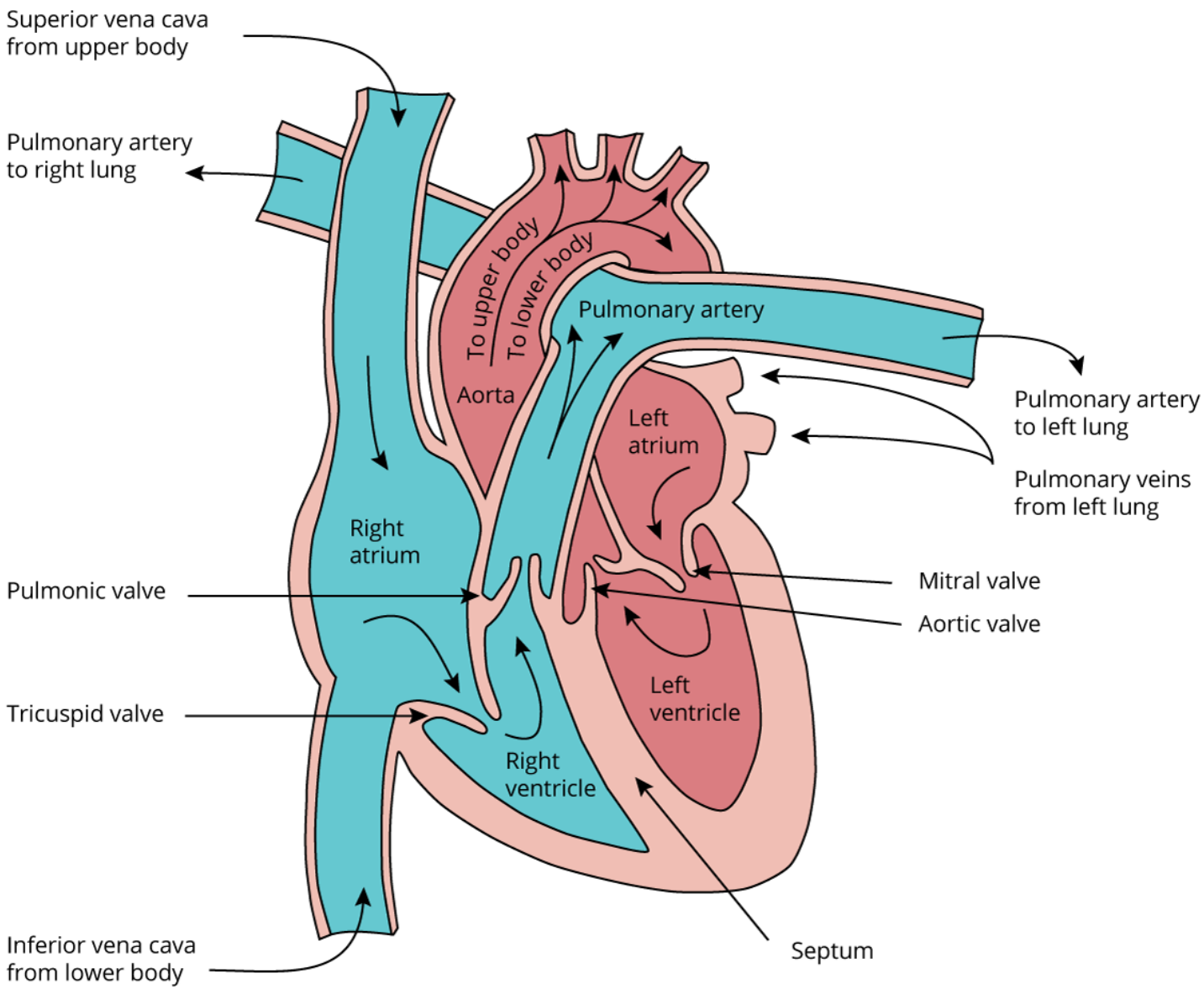
- Gynecomastia is the benign enlargement of the glandular tissue of the breast
- Caused by an absolute or relative deficiency of androgenic or absolute or relative excess of estrogenic action on breast tissue; androgens *per se* thus counteract its growth
- Absolute excess of estrogen likely the culprit in androgen users



Gynecomastia

- HAARLEM study: 7 % of subjects had gynecomastia at baseline and 19 % at the end of their cycle
- Users self-medicate with tamoxifen or aromatase inhibitors (letrozole, exemestane, anastrozole)
  - Tamoxifen in dosages of 10–20 mg daily shows efficacy in 80–90 % of cases from various causes and complete regression in about 60 %
  - Aromatase inhibitors show poor or modest results in various trial
- Some users believe certain androgens increase prolactin and cause ‘prolactin-induced‘ gynecomastia: no evidence to support this
  - Gynecomastia in hyperprolactinemia cases is secondary to its effect on sex hormones
- Some users believe certain androgens have progestin action on breast tissue and thereby cause gynecomastia: no evidence to support this
  - Notably, a male contraception study combining administration of testosterone with the potent progestin levonorgestrel noted no gynecomastia cases over a 6-month period

Cardiomyopathy



Cardiomyopathy

HAARLEM study results (3D echocardiography)

- 28.3 g increase in left ventricular mass (due to an increase in interventricular septum as well as posterior wall thickness)
- 1 mm increase in interventricular and left ventricle posterior wall thickness
- 4.9 % decrease in left ventricular ejection fraction
- -0.45 decrease in E/A ratio (suggests diastolic dysfunction; the left ventricle has a 'harder time' to get filled with blood)
- 9.2 mL increase in left atrial volume