Insight to the pathophysiology of microvascular angina

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- Definitions
- Pathology of coronary atherosclerosis in women
- Pathophysiology
  - Autonomic imbalance
  - Nitric oxide – Endothelin imbalance
  - Endothelial dysfunction
- Implication of conventional risk factors in women
- Summary

Typical case of microvascular angina in women

- 57-year-old postmenopausal woman
- Worsening angina pectoris
- Angina persisted despite use of diltiazem, nitrates, simvastatin, and imipramine.
- Risk factors included hypertension, overweight, and hypercholesterolemia.

Case presented in Circulation. 1999;99:1774

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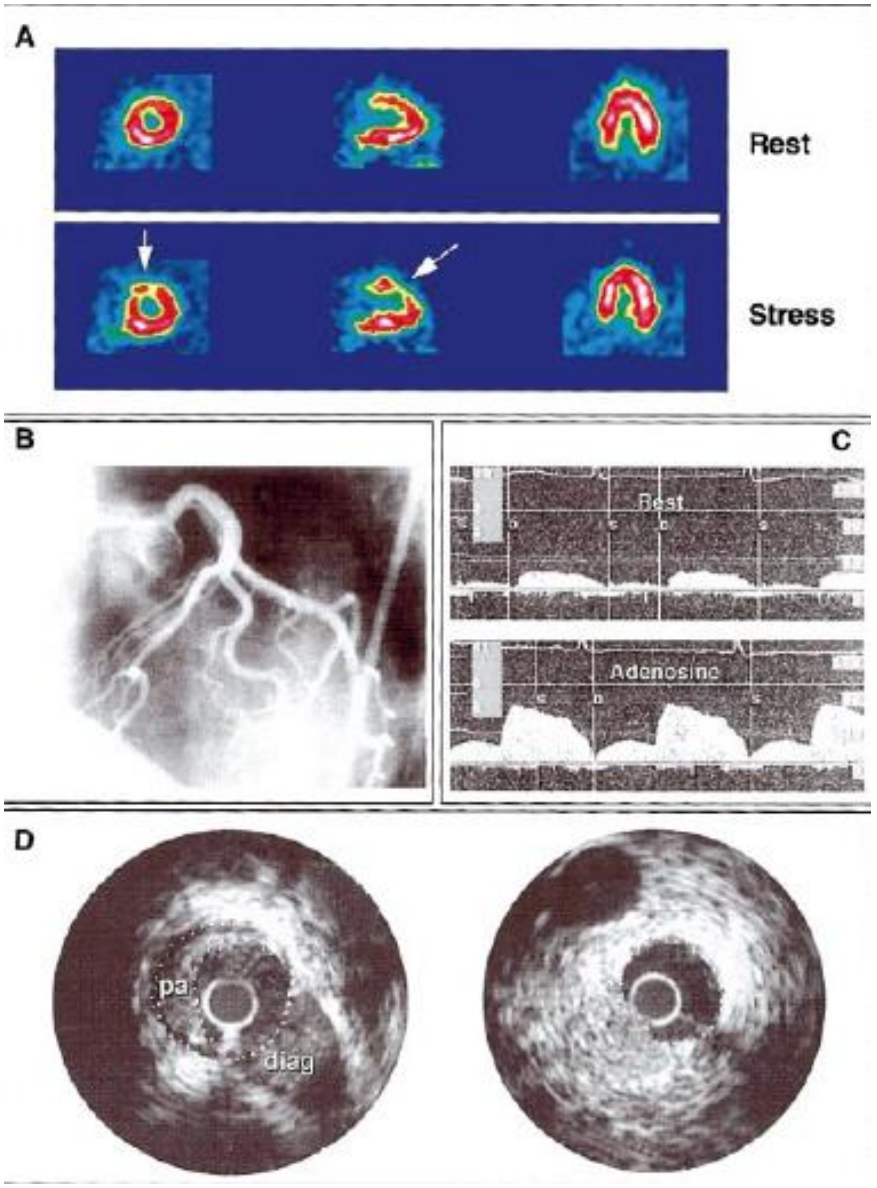
Diagnosis of microvascular angina made based on

- Angina
- Abnormal SPECT
- No obstructive CAD
- Abnormal coronary flow reserve and elevated LVEDP
- Diffuse atherosclerosis by IVUS



Women have a two-fold increase in “normal looking” coronary arteries in the setting of ACS

Table. Prevalence of “Normal” and Nonobstructive Coronary Arteries in Women Compared With Men

	No./Total (%)		
	Women	Men	*P* Value
Acute coronary syndrome			
GUSTO[2]	343/1768 (19.4)	394/4638 (8.4)	<.001
TIMI 18[3]	95/555 (17)	99/1091 (9)	<.001
Unstable angina[2]	252/826 (30.5)	220/1580 (13.9)	<.001
TIMI IIIa[6]	30/113 (26.5)	27/278 (8.3)	<.001
MI without ST-segment elevation[2]	41/450 (9.1)	55/1299 (4.2)	.001
MI with ST-segment elevation[2]	50/492 (10.2)	119/1759 (6.8)	.02

Abbreviations: GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MI, myocardial infarction; TIMI, Thrombosis In Myocardial Infarction.

Bugiardini and Bairey Merz JAMA 2005;293:477-84

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Pathophysiological gender differences: FRISC II

- 749 women and 1,708 men with unstable coronary artery disease
- Entry criteria = symptoms plus ischemia, defined as ECG change or + enzymes
- Randomized to early invasive versus noninvasive strategy
- Women were older, had fewer prior MI, better LVEF and lower troponin T levels

Lagerqvist et al, JACC 2001;38:41

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Women are less likely to have obstructive CAD BUT equally/more likely to die

	Female	Male
EF ≤45%	12%*	14%
No CAD	25%*	10%
LM/3 VD/2 VD/2 prox LAD	32%*	43%
Invasive (Death/MI)	12%	11%**

*p<0.05 vs men; ** P = 0.001 vs noninvasive

Lagerqvist et al, JACC 2001;38:41

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Differences in CAD presentation and findings in women compared to men

- Lower prevalence of MI
- More severe CHF
- More severe angina
- Less angiographic CAD
- More microvascular dysfunction?
- Abnormal vasomotor tone?
- More endothelial dysfunction?

Jacobs AK. Coronary revascularization in women in 2003: sex revisited. Circulation 2003. 107(3):375-377.

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Women have smaller coronary arteries

- After correcting for body surface area, womens' arteries are smaller
- This can seriously affect symptoms from anything that reduces diameter
  - Stenosis
  - Endothelial dysfunction

Adapted from Bellasi et al, New insights into ischemic heart disease in women. Cleveland clinic journal of medicine; 74: 585-594

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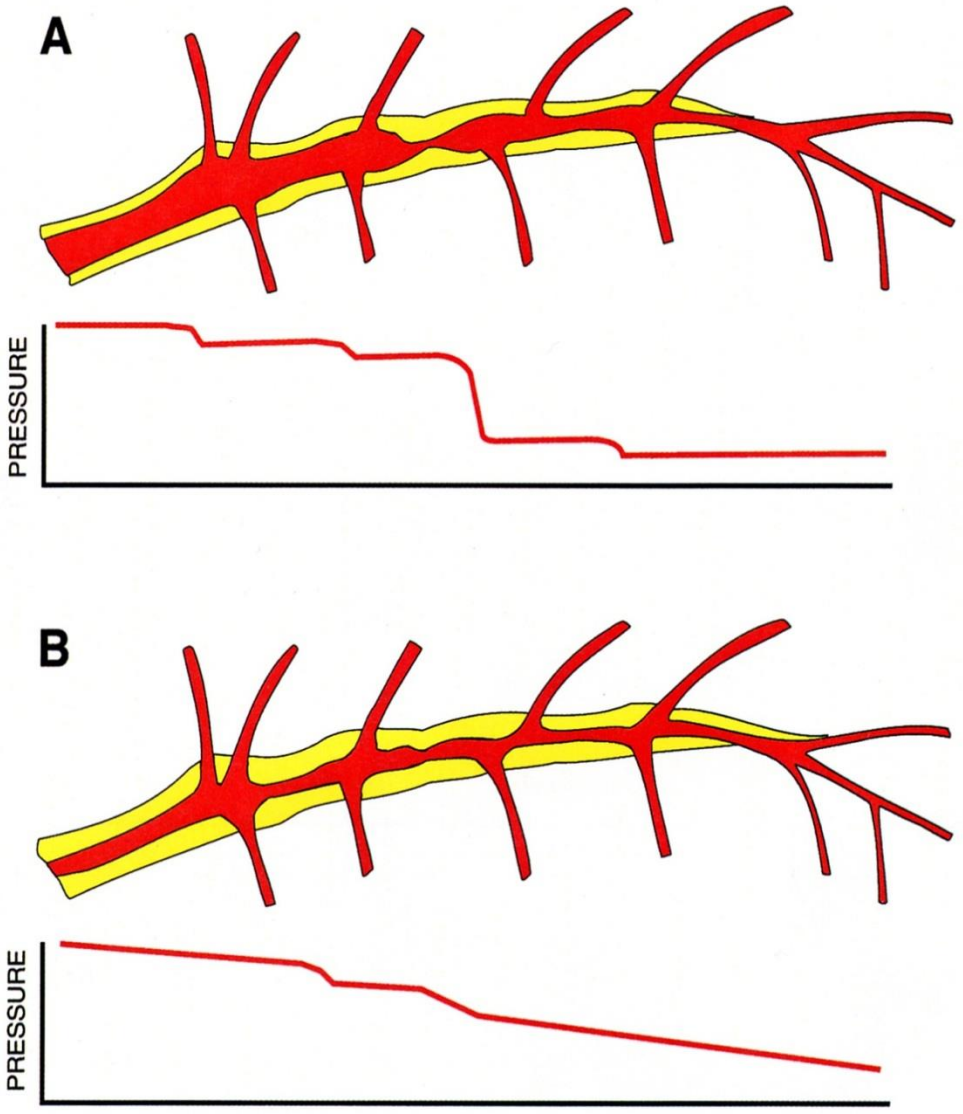
More diffuse atherosclerosis rather than focal lesion frequently observed in women



Coronary atherosclerosis in Women

- Women undergoing coronary angiography have
  - more diffuse atherosclerosis measured by IVUS,
  - more total compromised lumen adjusted for BSA throughout the arterial tree compared to men (WISE study)
- A consequence of more diffuse atherosclerosis might be more microvascular disease (limited flow reserve) that is not due to obvious obstructive disease

Two distinct plaque morphologies in sudden cardiac death

- Plaque rupture
  - thin fibrous cap over a large necrotic core
  - heavily infiltrated by foamy macrophages
  - 60% of thrombi in SCD
- Plaque erosion
  - thrombus over a base rich in VSMC with a proteoglycan-rich matrix
  - necrotic core is often absent
  - 40% of thrombi in SCD
  - In MI autopsy cohort, Women 37% vs Men 18%

Farb A, et al. Circulation. 1996. Arbustini E, et al. Heart. 1999

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Women suffer more plaque erosions compared to plaque rupture in men

Coronary thrombosis because of endothelial erosion.
A large nonoccluding thrombus adheres to the surface of an atherosclerotic plaque
Plaque erosion may lead to more acute coronary syndrome and NSTEMI

Coronary thrombosis because of plaque rupture.
A nonoccluding thrombus protrudes into the lumen of the artery through a break in the fibrous cap of a plaque

NEJM 1999

Plaque morphologies of SCD in women

- Plaque erosion
  - highly correlated with cigarette smoking
  - the most frequent type seen in women < 50 years
  - relatively little coronary arterial narrowing and less calcium plaque
- Plaque rupture
  - correlated with elevated serum total cholesterol
  - most frequent mode in women > 50 years
  - associated with severe stenosis and a large burden of calcium plaque

Burke AP, et al. Circulation. 1998

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Summary of microvascular angina in women

- Many women prone to more diffuse type of plaque in the smaller branches of arteries. It can escape detection by coronary angiography
- In coronary microvascular disease, plaque spreads evenly along artery walls so they appear normal instead of as clumps and visible blockages
- Women with recurring chest pain and abnormal stress testing but open arteries on CAG still be at high risk

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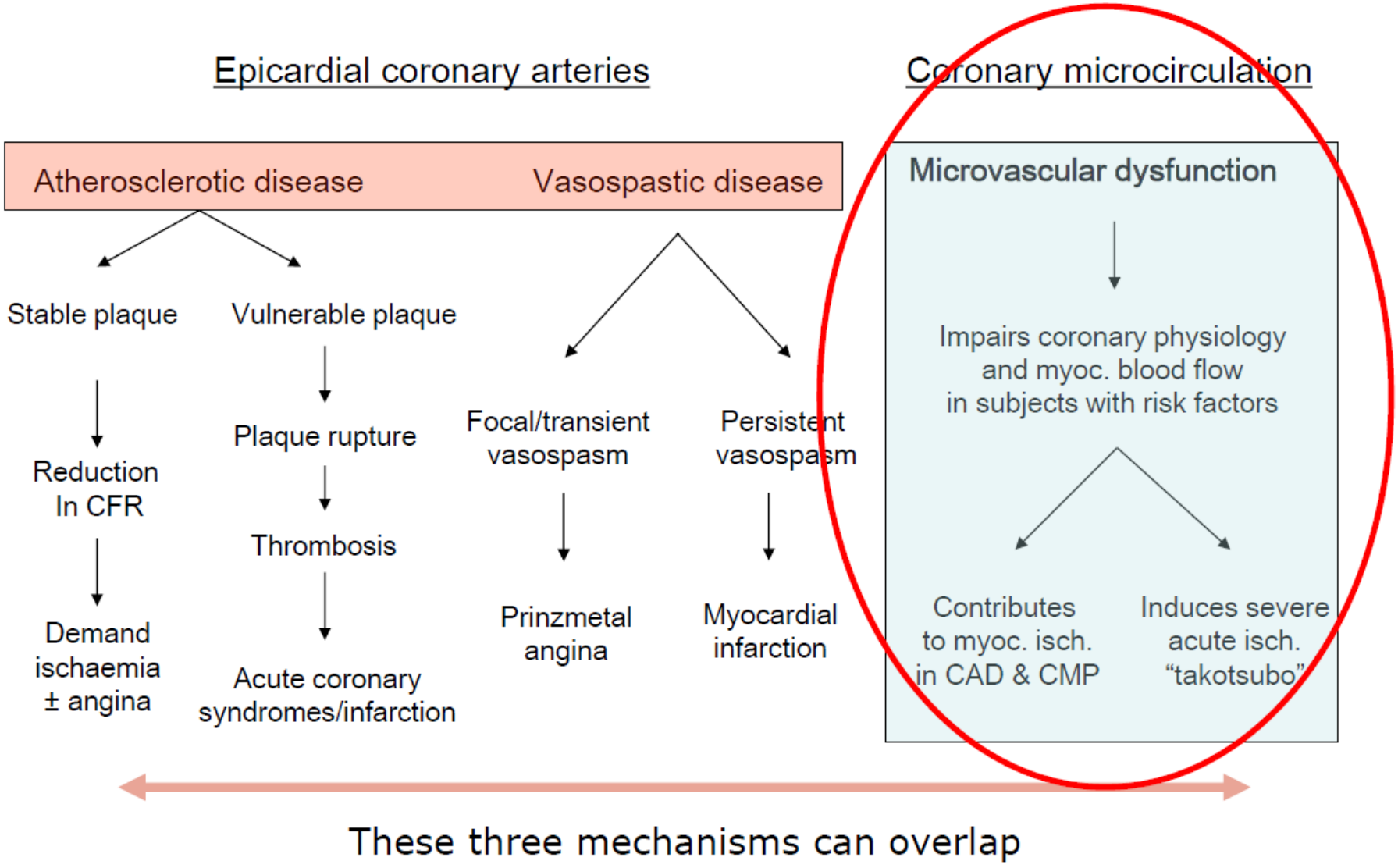
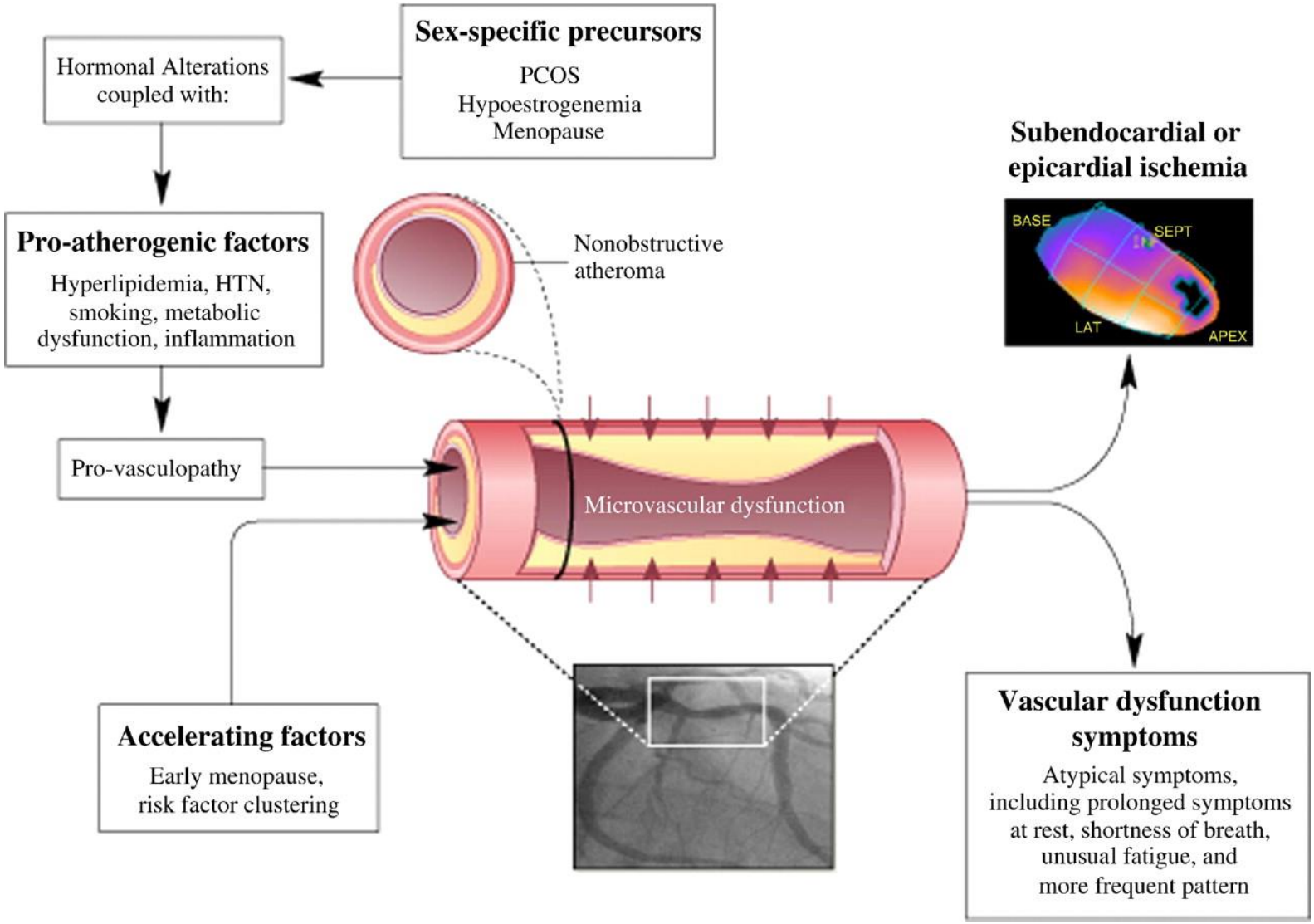
Mechanisms of myocardial ischaemia



Model of microvascular angina in women



Shaw, L. J. et al. J Am Coll Cardiol 2009;54:1561-1575

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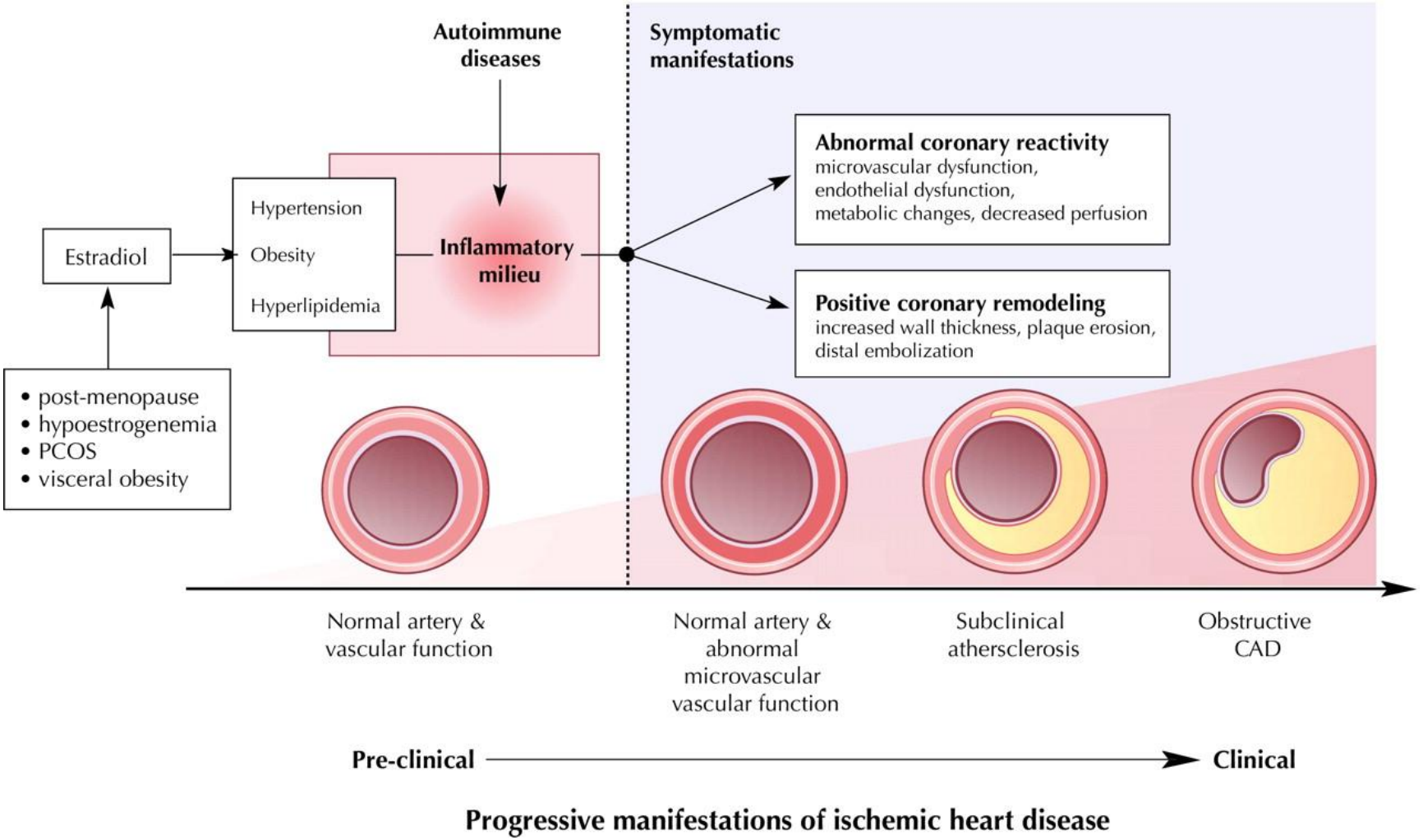
Suggested time sequence of ischemic heart disease development in women



Shaw, L. J. et al. J Am Coll Cardiol 2009;54:1561-1575

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Altered regulation of coronary microcirculation

- 40 - 50% of flow resistance in main coronary arteries determined by microvascular system (Cannon. JACC 2009).
- Endothelial dysfunction
  - abnormal release of, or response to, vasodilators (such as nitric oxide) or vasoconstrictors
- Inflammation
  - higher levels of CRP in microvascular angina patients
- Microcirculation abnormalities
  - Reduction in coronary blood flow reserve
  - Increase in arterial resistance
- Han SH, Bae JH et al. examined patients with obstructive CAD by conducting simultaneous IVUS and assessment of coronary reactivity (Eur Heart J 2008).
  - Men had more atheroma burden
  - Women had more disease of the microcirculation.

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Altered regulation of coronary microcirculation: Autonomic imbalance

- Abnormal cardiac adrenergic nerve function detected in 75% of microvascular angina patients (Lanza et al. 1997).
  - Norepinephrine spillover and enhanced adrenergic drive
  - ↑ microvascular tone and sensitize small coronary arteries to vasoconstrictor stimuli
  - Reduction of CFR and heterogeneity of myocardial perfusion
- Women have a delayed norepinephrine reuptake at the synapse level, (Schroeder et al. 2004).
- Parasympathetic tone also impaired in 2/3 of microvascular angina patients compared to normal controls (Gulli et al, 2001)
- Autonomic dysregulation related with vasospasm in variant angina, further supporting both sympathetic and parasympathetic imbalances as a cause of chest pain (Inazumi et al. 2000).
- Identification of autonomic impairment potentially important in therapeutic strategies aimed at increasing vagal tone, such as aerobic exercise (La Rovere et al. 1994)

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Altered regulation of coronary microcirculation: NO-Endothelin imbalance

- Imbalance between the endothelial derived nitric oxide (NO) (vasodilator) and endothelin-1 (ET-1) (vasoconstrictor).
- ↓ bioavailability of endogenous NO and ↑ plasma ET-1
  - Significantly higher plasma ET-1 levels observed in patients with microvascular angina (Cox et al. 1999)
  - An abnormal response to ET-1 also observed in microvascular angina even though its plasma concentration not elevated (Newby. 1998)
- Genetic abnormality underlying altered endothelial production of NO recently suggested.
  - Lower frequency of intron 4aa in eNOS polymorphism in microvascular angina patients, suggesting protective effect (Sinici. 2010).

Endothelial dysfunction

- In large arteries, endothelial dysfunction considered among the earliest changes associated with atherosclerosis before structural changes of the vessels (Schachinger et al. 2000)
  - Predictive of future obstructive CAD (Bugiardini et al. 2004).
- Endothelial dysfunction correlated with reduced CFR during dipyridamole (Cannon 1988) or acetylcholine (Egashira. 1993), pacing (Quyyumi. 1992), or cold exposure (Zeiher et al. 1995).
- Altered circulating EPCs constitute an underlying contributing factor to endothelial dysfunction encountered in patients with microvascular angina (Huang et al. 2007).

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Endothelial dysfunction

- Endothelial dysfunction observed in diabetes, CAD, congestive heart failure, and chronic renal disease.
  - Also in MetS, dyslipidemia, obesity, smoking, and even sedentary lifestyle without overt cardiovascular disease.
- Sex hormones may affect vascular constriction and dilation
  - Women may be at increased risk of microvascular disease because of a history of fluctuating hormone levels (puberty, pregnancy, and menopause).
  - Although estrogen may help to delay the development of atherosclerosis in the major arteries, this protection may not extend to the microvascular system.

Potential explanation based on estrogen in plaque erosion

- Estrogen reduces cellular hypertrophy and enhances vessel wall elasticity
  - possibly contributing to less lumen intrusion for the same amount of atherosclerosis
- Estrogen reduces smooth muscle cell migration and lower collagen deposition in response to injury
  - leading to thinner fibrous plaque in women
- Estrogen and progesterone upregulate degradative collagenases and inflammatory markers (hsCRP)

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4 risk factors having higher impact on women

- In general, CV risk factors are gender-blind.
- HOWEVER, when taking a closer look, four risk factors affect women more than men
- And, what might those big 4 be?

Cigarette smoking

Diabetes mellitus

High triglycerides and low HDLs

Hypertension

Women-smokers have higher risk than men-smoker

- Women who smoke have their first heart attack 19 years earlier than women who don't smoke
- Women smokers are 2-5 times more likely to have a heart attack than women who don't smoke
- When a woman quits smoking the risk of CHD drops substantially in only 2-3 years, reaching baseline after ten years
- Patients who cut down but continue to smoke 1-4 cigarettes / day continue to have elevated risk of CHD

Diabetes creates higher risks for women with CAD

- Diabetes increases CAD risk
  by 3 - 7-fold in women vs 2-3-fold in men
- Diabetes doubles the risk of second heart attack in women but not in men
- In a large cohort referred for coronary disease, diabetic women had the highest mortality rates
- Framingham Heart Study
  - Women with diabetes mellitus had relative risk of 5.4% for CAD vs women without diabetes
  - Men with diabetes had relative risk of 2.4%

American Heart Association, Centers for Disease Control and Prevention
Manson JE, et al. Prevention of Myocardial Infarction. 1996
Giri S, et al. Circulation. 2002

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Lowest survival rates for diabetic women

	Death			Death/MI		
	0-VD	1-VD	≥2-VD	0-VD	1-VD	≥2-VD
Diabetic men	93.8	93.0	91.3	86.3	77.0	79.0
Nondiabetic men	99.0	96.5	95.0	93.8	88.0	85.0
Diabetic women	99.0	80.0*	81.3*	96.5	72.5*	60.0*
Nondiabetic women	98.8	97.5	97.0	95.5	85.0	77.5

****P* < .05. Extent of ischemia was determined by the number of vascular territories (0, 1, or 2 vessels) involved in the reversible perfusion defect.**

Giri S, et al. *Circulation.* 2002

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Impact of metabolic abnormality in women

- Higher prevalence of metabolic risk factors
  - ↑ blood cholesterol
  - ↑ physical inactivity
  - ↑ overweight (body mass index, 25.0-29.9)
  - ↓ HDL cholesterol levels more predictive of CAD2

1. American Heart Association. *1999 Heart and Stroke Statistical Update.* 1998
2. Mosca L, et al. *Circulation.* 1999

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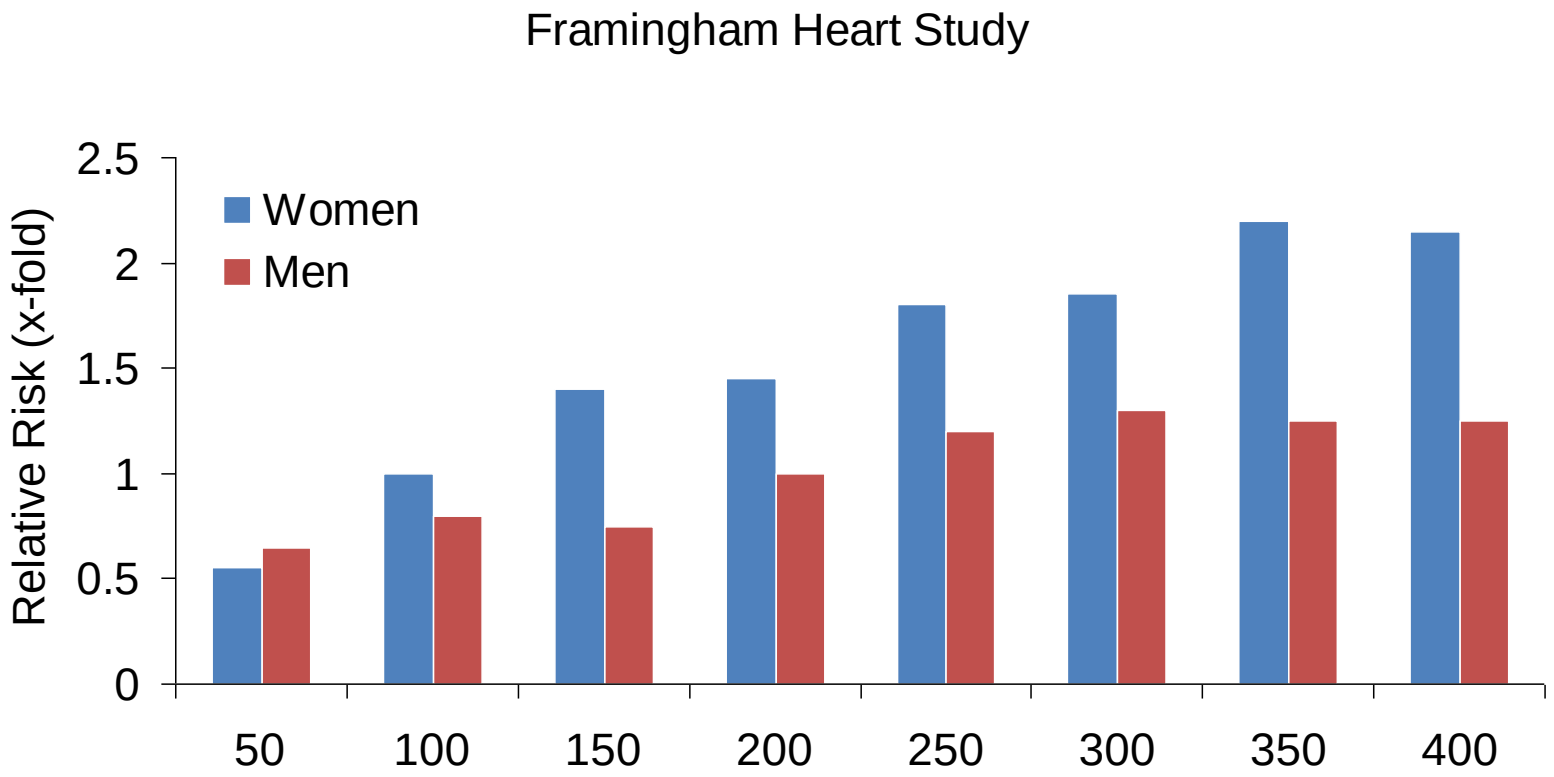
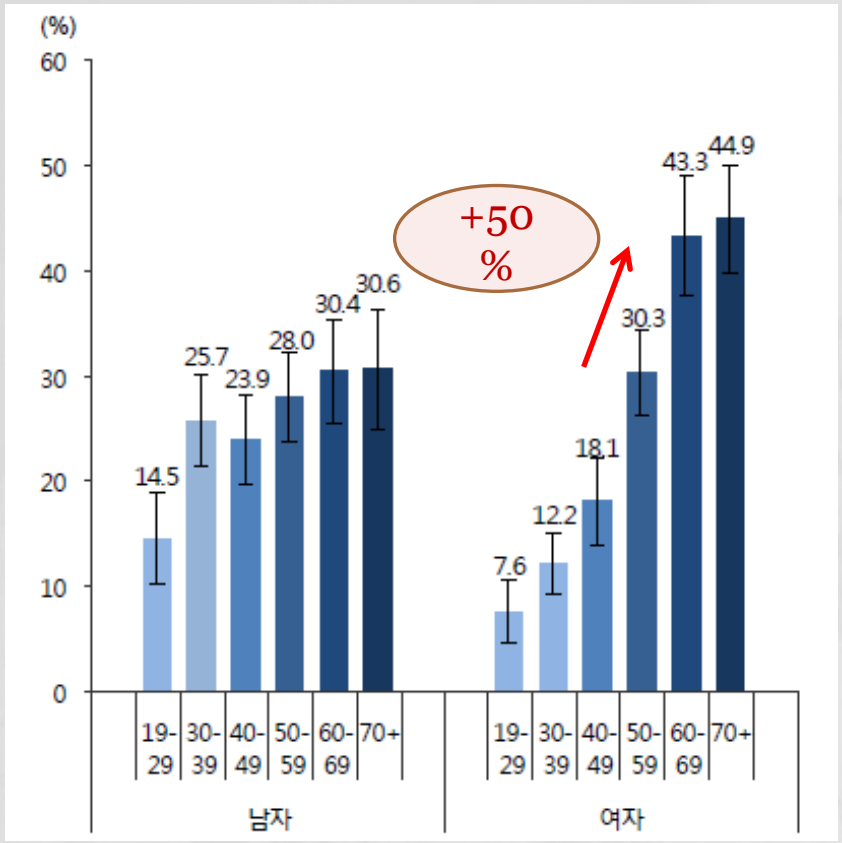
Impact of triglyceride levels on relative risk of CAD

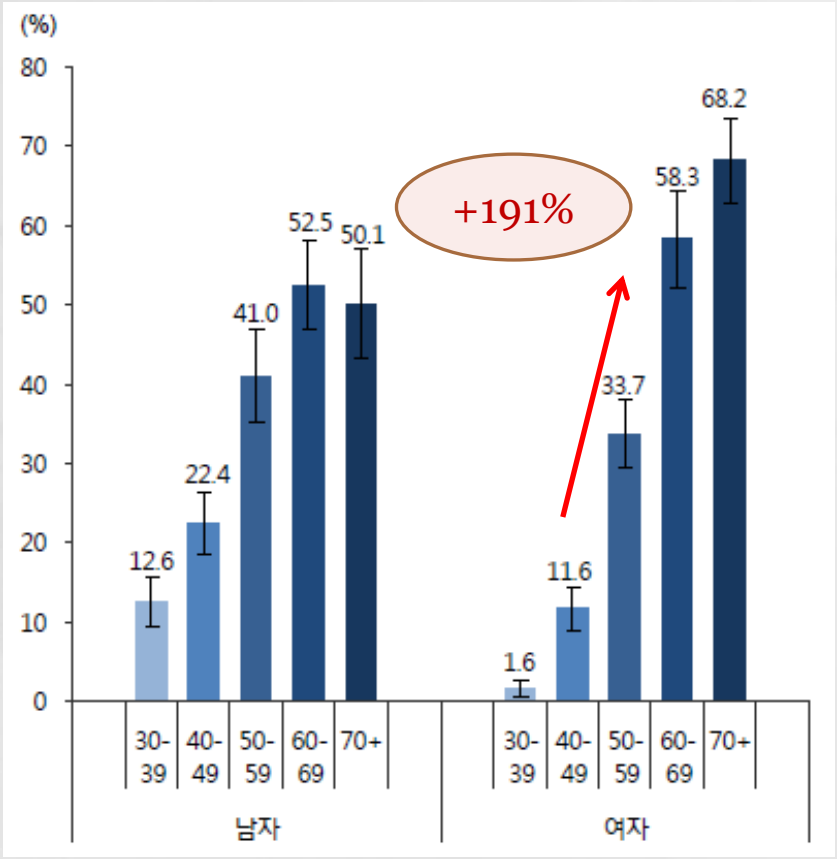


Castelli WP. *Can J Cardiol.* 1988

폐경 전후 여성에서 비만률, 고혈압 유병률 증가 현상



중년 여성에서 비만률 50% 증가



중년 여성에서 고혈압 유병률 191% 증가

폐경 전후 여성에서 고혈압 발생의 위험 요인 분석 (안산-안성 코호트)

- 폐경 여성의 평균 폐경 연령: 47.8 ± 5.3 yrs
- 2기 추적 검사 문진에서 폐경 유무에 따른 고혈압 유병률
- 42세 – 52세의 여성을 대상으로 분석
- 폐경 인구의 연령이 2.5세 높음

  : 47.6 ± 2.4yrs VS 45.1 ± 1.9yrs

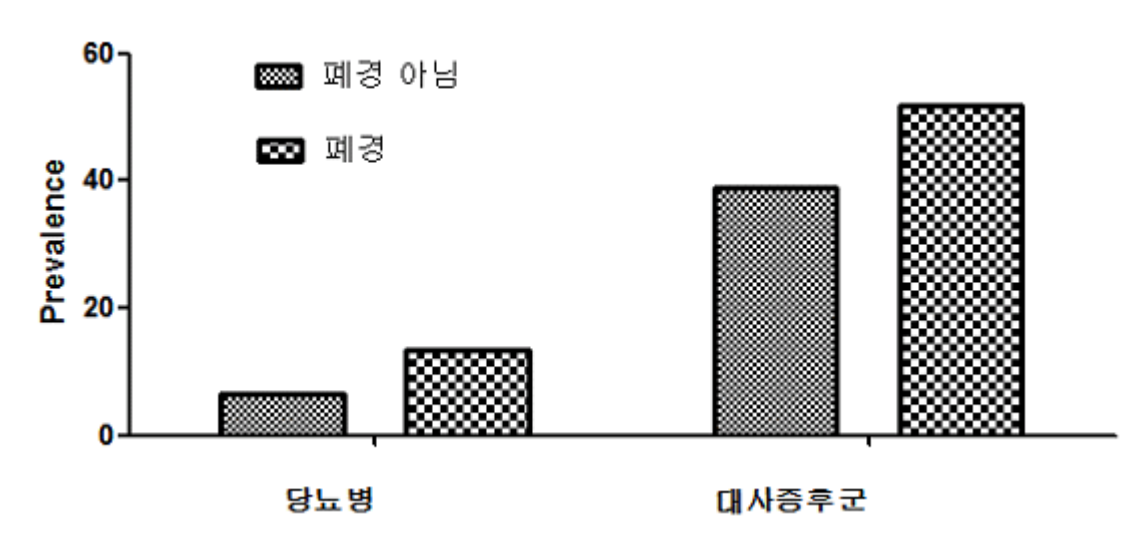
			고혈압	전기고혈압	정상	전체
폐경	폐경 아님	빈도	103	125	399	627
		폐경 중 %	16.4%	19.9%	63.6%	100.0%
	폐경	빈도	176	171	367	714
		폐경 중 %	24.6%	23.9%	51.4%	100.0%
전체		빈도	279	296	766	1341
		폐경 중 %	20.8%	22.1%	57.1%	100.0%

폐경 유무 인구 비교

	폐경 여부			
	유(n=715)		무(n=628)	
	평균	표준편차	평균	표준편차
연령	47.64	2.429	45.12	1.854
알코올 섭취량	1.43	6.560	1.92	5.766
몸무게	59.78	7.717	59.62	7.876
신장	155.15	5.207	155.31	5.149
체질량 지수	24.85	2.946	24.76	3.068
2차 추적 조사 시 수축기 혈압	112.76	15.153	109.01	13.938
2차 추적 조사 시 이완기 혈압	76.38	9.607	73.89	10.343
2차 추적 조사 시 허리둘레	82.76	8.786	80.70	8.479

연령, 체질량지수, 허리둘레를 보정하여도 폐경은 고혈압의 위험률을 30% 증가시켰음

폐경 인구에서 대사증후군 유병률이 높음

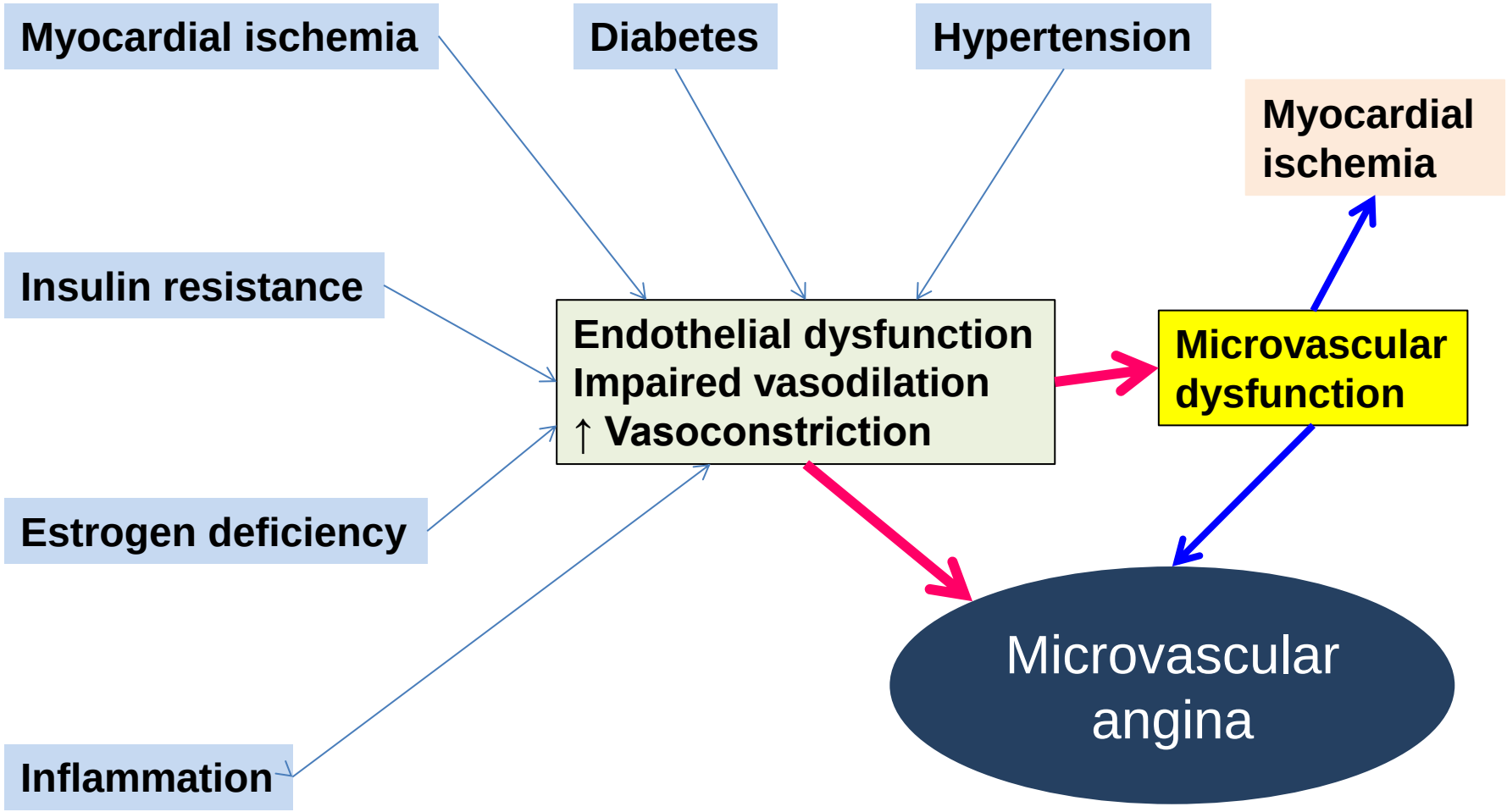


- 당뇨병과 대사증후군 역시 폐경 인구에서 6.5% 대 13.3%, 38.9% 대 51.7%로 크게 증가
- 이를 multivariate analysis에 추가하였을 때 폐경 요인의 상대 위험도가 의미 없는 것으로 나타나 폐경에 의한 고혈압 발생은 대사 증후군의 증가에 의해 매개되었을 가능성이 있음

Summary and Conclusion

- Women with cardiac chest pain indicated of myocardial ischemia in the absence of obstructive coronary arterial disease are often diagnosed as microvascular angina.
  - > 2/3 of women undergoing coronary angiography for angina will have ‘normal looking’ coronaries or non flow-limiting disease.
- Women may have a higher frequency of coronary plaque erosion and microembolization rather than classical plaque rupture, resulting in greater microvascular dysfunction.
- A significant proportion of these patients have abnormalities of vascular function (endothelial dysfunction), coronary flow reserve (microvascular disease), or both.
- Diabetes and metabolic abnormality are a more powerful risk factor for CAD in women than in men, warranting intensive risk factor control.

Pathophysiology of microvascular angina



Thank you for your attention.