Current perspectives

Female gender, myocardial remodeling and cardiac failure: are women protected from increased myocardiocyte apoptosis?

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Heart failure appears to be less common and less severe in females, and elderly women have a better overall survival after myocardial infarction than males and also a decreased risk of arrhythmic death. Human and animal studies also show that females display more favorable cardiac remodeling in several experimental and clinical conditions. However, the underlying pathophysiologic mechanisms have not been established, even though estrogens, beta-adrenergic stimulation, the renin-angiotensin system, and a greater resistance to myocardiocyte apoptosis in females have been proposed as hypothetical contributing factors. Indeed, epidemiologic, experimental and clinical evidence of gender differences in myocardial remodeling and heart failure favoring women could prompt the use of female myocardial progenitor or stem cells for cellular replacement therapy in cardiac failure, on the premises of a greater protection from myocardial apoptosis and unfavorable remodeling in women.

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Introduction

Cardiovascular disease is the most common cause of mortality and morbidity in developed countries, and both men and women are often afflicted by heart disease. However, many data show that cardiovascular disease, and particularly heart failure, seems to strike men more severely and more commonly than women (Fig. 1). Despite the many conceptual, methodological and logistic difficulties involved in the study of the role of gender in cardiovascular disease, the thorough appraisal of the sex-related clinical differences and underlying pathophysiologic mechanisms, and in particular of the protective mechanisms specific to women, may improve the understanding and management of heart disease leading to benefits for both sexes[1].

In the present article we review the main epidemiologic, pathophysiologic and clinical data regarding the role of gender in cardiac remodeling and failure, with emphasis on the apparent more favorable course in females.

Epidemiologic evidence

The incidence, prevalence and severity of cardiovascular disease are different between men and women[1,2] (Fig. 1). Specifically, women seem to be relatively protected from atherosclerosis until menopause, and they thus usually present with symptomatic atherosclerotic disease much later than men[3]. Moreover, many studies show that there are very important differences between men and women in many cardiovascular clinical conditions and in particular in heart failure[4]. Recently, this Journal has devoted a series of thorough viewpoints on these issues[2,5-9]. Nonetheless, a brief discussion of the epidemiological and clinical evidence of the gender-related differences in cardiovascular disease is appropriate in this context in order to fully understand the underlying pathophysiologic mechanisms.

Despite several conflicting reports, heart failure seems to be less common and less severe in women, at least when populations at risk are extensively adjusted for the relevant covariables. Indeed, remote reports such as the Framingham and the NHANES-I studies had suggested an overall decreased incidence and severity of heart failure in women[10,11]. However, over the years the picture has become much more complex. Indeed, other large surveys suggested an increased prevalence of heart failure of unspecified diagnosis in women,

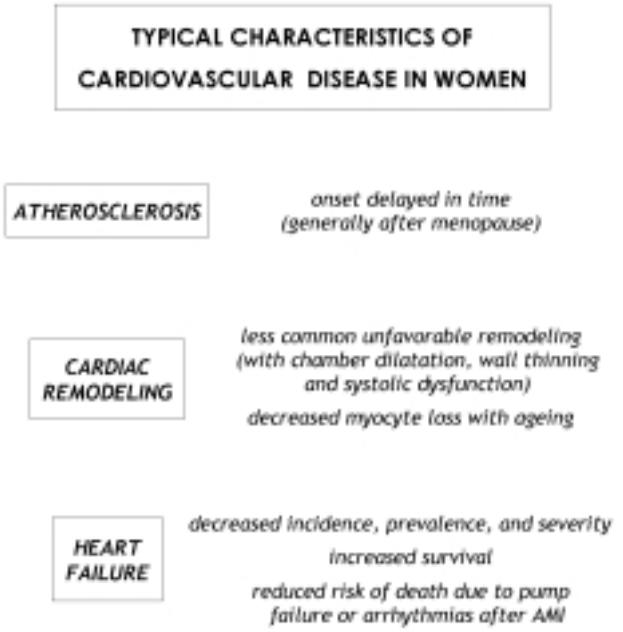

Figure 1. *Typical characteristics of atherothrombotic disease, cardiac remodeling and heart failure in women in comparison to men. AMI = acute myocardial infarction.*

at least when age and comorbidities were not fully taken into account[5]. On the other hand, a recent 5-million subject wide survey from the American Heart Association confirms previous findings and shows a lower prevalence of heart failure in women vs men (1.9 vs 2.5%)[3].

Such broad comparisons must however be considered with caution, as cardiac failure may be viewed as a heterogeneous condition and as the final common pathway of several distinct pathologic conditions[6]. In fact, several studies, including the pivotal one from Framingham, reported different incidences of the various subtypes of heart failure in men vs women, as males were more often affected by ischemic cardiac failure while females suffered more commonly from valvular and hypertensive cardiomyopathies[10,12]. Nonetheless, well-designed epidemiologic studies that have closely examined the link between gender and heart failure by employing advanced multivariable statistical modeling have concluded that the prognosis is better in females with heart failure rather than in men, even after stratification or adjustment for the underlying cause of cardiac failure[6,12,13]. The Olmsted County community study also supported these findings by showing a higher prevalence of a preserved left ventricular function among women with post-infarction heart failure vs men[14], and similar findings have been reported in a recent 19 710-patient study based on the US Medicare database[15].

Updated population-based and clinical studies have thus confirmed the significant and independent role of gender in the risk of developing ischemic cardiomyopathy as well as its short- and long-term prognoses, with particular emphasis on systolic dysfunction and unfavorable left ventricular remodeling[12]. Cohort studies of several hundred survivors of acute myocardial infarction have in fact shown that elderly women have better mid and long-term survivals than males, even though they undergo surgical or interventional coronary revascularization less frequently, are less likely to receive optimal medical therapy than men, and, probably in part as a consequence of the former factors, their unadjusted in-hospital mortality appears increased[6-9,16,17]. Conversely, younger women appear at the highest risk of death and post-infarction adverse events[18]. These findings are in line with those of other authoritative surveys, such as, for example, that of the American Heart Association which shows an unadjusted 2-fold higher rate of post-infarction heart failure in women vs men (46 vs 22%)[3]. Nonetheless, this finding strikingly changes direction after stratification according to age, as over the different age strata women are always less likely to experience heart failure than men[3]. Moreover, because of the greater number of elderly women, the prevalence of heart failure appears inflated in females. Finally, in the very same American Heart Association sample, it is clear that once heart failure has been diagnosed, survival is significantly better in women than in men.

In addition, while women have a decreased rate of death due to pump failure[13] as well as a decreased risk of post-infarction arrhythmic death[19], other apparently conflicting findings should be borne in mind, including the increased incidence of post-infarction cardiac rupture in females treated with thrombolysis[20], the potentially less favorable response to thrombolytic therapy[21], the higher unadjusted in-hospital mortality[18], and the increased risk of cardiogenic shock[17]. On the other hand, such unfavorable features which are characteristic of women are partially offset by the decreased out-of-hospital case fatality typical of acute myocardial infarction in females[5]. Indeed, among 201 114 Scottish patients with myocardial infarction, younger women admitted to the hospital had a higher 30-day mortality than men[22]. However, when the comparison was made without undue exclusion of patients dying before arrival to the hospital and after having adjusted for age, females were overall more likely to survive to 30 days than males (adjusted $p < 0.0001$). Anyway, confirming the need for caution in extrapolating the above evidence to our real life patients, the recent IN-CHF Registry did not show any gender differences among the 3327 enrolled patients[23].

More than a word should be spent on the issue of the optimal diagnostic and therapeutic management of women's cardiovascular disease, with particular emphasis on the specific effects of several interventions, drugs and strategies. This issue has indeed been recently thoroughly discussed in this Journal[6-9]. Nonetheless, it is sufficient to say that most of the interventions of proved value in the overall population are of major benefit and impact in females too, including beta-blockers,

angiotensin-converting enzyme inhibitors, coronary revascularization and antithrombotic therapies. Cardiac rehabilitation and exercise training, which have been recently proved to significantly improve prognosis in patients with cardiovascular disease[24], are also markedly beneficial in women, even though unfortunately there is evidence that selection biases partially limit access of female patients to rehabilitation programs even when they are strongly indicated[25].

Cardiac remodeling in women

Clinical studies in humans and experimental studies in animals have shown that females display more favorable and adaptive patterns of cardiac remodeling in a wide range of clinical and laboratory conditions. Indeed, the cardiac response to overload or injury consists in adaptive or maladaptive processes potentially leading to unfavorable left ventricular remodeling (e.g., systolic dysfunction and cardiac dilation). These remodeling processes are typical of human ischemic, valvular or hypertensive cardiomyopathies (Fig. 2). The clinical differences between men and women are probably due, at least in part, to such specific patterns and mechanisms of cardiac remodeling.

Experimental studies in rats show that males exposed to chronic pressure overload more frequently have unfavorable remodeling with a depressed systolic function in comparison to females[26]. In a different rat model of volume overload, males had a 10-fold higher mortality rate than females, and the latter much more rarely showed signs of congestive heart failure[27]. Moreover, pressure overload after anterior myocardial infarction induces concentric ventricular hypertrophy in female rates while causing cardiac dilation and infarct expansion in males[28].

In a human clinical study using echocardiography to assess the left ventricular mass and contractile function, women developed unfavorable cardiac remodeling less frequently than men[29], and in a thorough study in patients with aortic stenosis of similar severity evaluated by means of cardiac catheterization, and at similar degrees of afterload, women displayed more favorable left ventricular remodeling than men, who typically showed a decreased systolic and max dP/dt[30].

Pathophysiologic mechanisms of cardiac failure in women and the role of apoptosis

The pathophysiologic mechanisms underlying the differences in the remodeling processes and clinical outcomes between men and women have not yet been completely established (Fig. 2). Nonetheless, several putative mechanisms and hypothetical etiologic factors have been proposed, including a different expression and activation of the transcription factors Akt and nuclear factor-kappaB between genders[31], as well as an increased activity of telomerase in women[32] (Table I).

Moreover, the attention of basic researchers has also focused on the mechanisms of synthesis and on the effects of nitric oxide, on beta-adrenergic activity, and the cellular transduction system and the renin-angiotensin system[33,34].

A very interesting field of research currently underway involves the appraisal of the role of estrogen on myocardial cells[35-37]. This appears even more interesting in the light of evidence of intracellular myocardiocyte synthesis of estrogens and the potentially antiapoptotic actions of these hormones[38]. Moreover, the activity of estrogen receptors also seems to protect the heart from ischemia-reperfusion injury[39], and this effect may be at least in part due to a reduction in my-

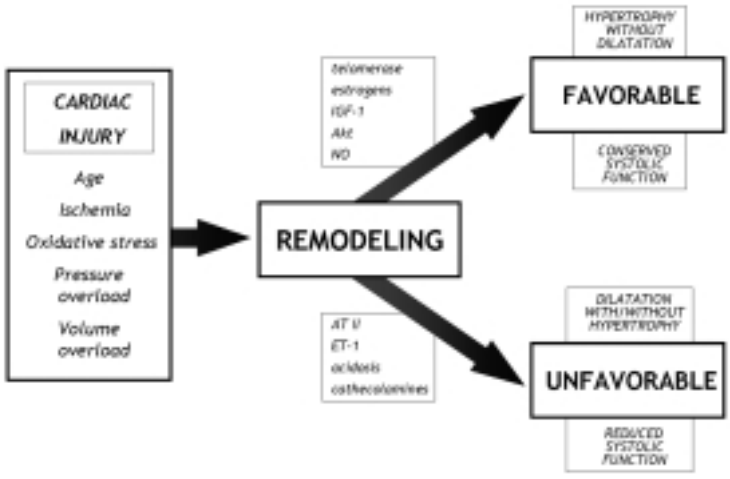

Figure 2. *Myocardial damage and pathophysiologic mechanisms of the response to injury may lead to favorable cardiac remodeling or eventually overcome cardiac adaptive processes thus causing unfavorable left ventricular remodeling. AT II = angiotensin II; ET-1 = endothelin-1; IGF-1 = insulin-like growth factor-1; NO = nitric oxide.*

Table I. Gender differences in cardiac remodeling and potential underlying pathophysiologic mechanisms.

Mechanism	Typical findings in females	Effect on cardiac remodeling	Effect on myocardiocyte apoptosis
ACE-2 activity	? Increased (dizigosity)	More adaptive remodeling	+/-
Akt activity	Increased	Upregulation of IGF-1 and survival signals	-
Arrhythmogenicity	Decreased	Decreased risk of arrhythmic clinical events	NA
Beta-adrenergic expression	Decreased	Protection from unfavorable myocardial and systemic effects due to beta-adrenergic hyperactivity	+
IGF-1 activity	Increased	Favors survival and cell replication	-
Intramyocardiocyte estrogen synthesis	Increased	Upregulates transcription factors	-
NO synthesis	Increased	Favors ischemic preconditioning and may inhibit apoptotic cascade	-
Resistance to ischemia	Increased		-
Telomerase activity	Increased	Favors survival and cell replication vs death	? -

ACE = angiotensin-converting enzyme; IGF-1 = insulin-like growth factor-1; NA = not applicable; NO = nitric oxide. + increased; - decreased; +/-variable effect.

ocardiocyte programmed cell death[40]. On the other hand, the complex impact of estrogen replacement therapy after myocardial infarction was demonstrated by Smith et al.[36], who showed how in ovariectomized female animals early estrogen therapy increased infarct size and infarct extension while later onset estrogen replacement could normalize wall tension and inhibit cardiac dilation. To complicate matters further, van Eickels et al.[37] have recently shown that estrogen therapy after myocardial infarction in ovariectomized female mice may, on the one hand reduce myocardial apoptosis and infarct size, but on the other is strikingly associated with unfavorable remodeling and an overall increased mortality.

Indeed, there is still uncertainty on the relative weight of these mechanisms and whether any of them has a significant impact on the clinical and remodeling differences between males and females observed in humans. Most likely, many different systems and mechanisms simultaneously play a role as casual factors, sometimes counteracting each other in a balanced effect and other times acting in one direction only with a synergistic effect.

Nonetheless, myocardiocyte apoptosis definitely plays an important role among the mechanisms responsible for myocardial adaptation as well as unfavorable ventricular remodeling. In fact, apoptotic progressive loss of myocardiocytes has been implicated as a major factor in the transition from favorable to adverse cardiac remodeling, leading ultimately to end-stage heart failure, in both animals and humans[41-43].

Apoptosis, or programmed cell death, represents a mechanism of "suicidal" cell death, leading, through an active and adenosine triphosphate-dependent process, to cell death in a highly controlled manner and usually in the absence of any nearby inflammation[44]. Apoptosis may occur in cells, including myocardiocytes, as a last resort response to detrimental stimuli such as ischemia, oxidative damage, acid or alkaline stress, cellular stretching, as well as neurohumoral (i.e., beta-adrenergic and renin-angiotensin system) hyperactivation[42] (Fig. 3).

Several animal experiments and human clinical studies have shown that apoptosis plays a critical role in many pathophysiologic conditions and, in particular, in the earlier as well as later phases of acute myocardial infarction[43,45-47]. However, myocardiocyte apoptotic rates vary widely and strongly depend on several different clinical, pathologic and pathophysiologic factors, even though shortly after myocardial infarction apoptosis may involve up to 7-25% of cells in the peri-infarct regions[43,46,47].

Interestingly, recent evidence shows that gender may influence the apoptotic cascade and modulate the rate of apoptotic cell loss after a myocardial infarction. Indeed, cardiac aging is associated with preservation of the ventricular mass and the total number of myocardiocytes in women, while in men there is a continuous and apparently unavoidable loss of myocardiocytes equivalent to approximately 1 g per year[48]. Moreover, similar findings have been reported in rats and they seem to be correlated with the expression of insulin-like growth factor-1, a well-known antiapoptotic factor, potentially acting through the Akt pathway[49].

More recently, it has been demonstrated that myocardial apoptotic rates in women are significantly lower than in men, both in humans dying of non-cardiac causes[50], and in patients with end-stage heart failure at the time of heart transplant[51].

Some mechanisms could indeed offer a unified explanation of both apoptosis-modulation and gender differences in cardiac remodeling. Specifically, estrogens have been proved as a potential antiapoptotic mechanism explaining such differences[40]. However, the inclu-

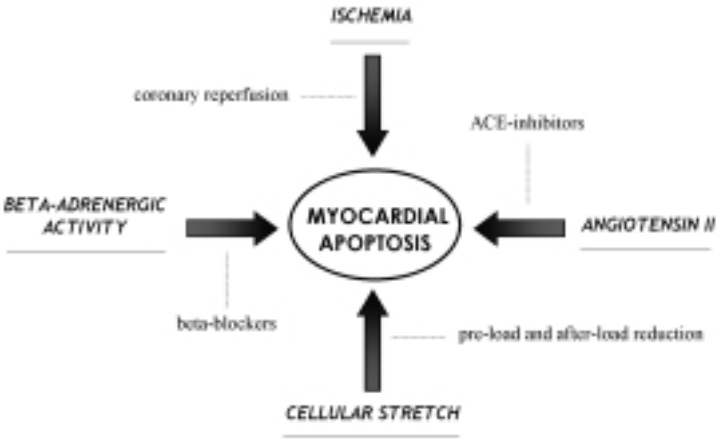

Figure 3. *Major pro-apoptotic stimuli known to modulate the myocardiocyte balance between survival and cell death due to apoptosis (*dashed lines *represent antiapoptotic factors or therapeutic agents). ACE = angiotensin-converting enzyme.*

sion in the available studies of elderly women likely to be post-menopausal casts a shadow of caution on this hypothesis[52]. On the other hand, an increased intramyocardial synthesis of estrogens in women, well after menopause, might be the mechanistic link of this phenomenon.

However, the role of gender in the modulation of post-infarction myocardial apoptosis and the potential underlying mechanisms have not been well established. Nonetheless, preliminary data support a favorable effect of female sex on post-infarction myocardial apoptosis and on the expression of the pro-apoptotic factor bax, such that women dying after acute myocardial infarction appear to have 10-fold lower apoptotic rates than men, as well as a significantly decreased peri-infarct expression of bax[53]. Moreover, in this small study, female gender, reduced apoptosis and bax expression after myocardial infarction seemed to be associated with more favorable post-infarction remodeling (i.e., lesser wall thinning and chamber dilation), supporting the potential cause-effect link between female sex, increased myocardiocyte resistance to pro-apoptotic stimuli and adaptive remodeling after infarction[52]. In fact, these preliminary findings appear in line with experimental evidence showing that female rat cardiac fibroblasts appear to resist much longer to ischemic injury than fibroblasts deriving from male hearts, and this resistance is mainly related to reduced apoptotic rates in female cells[54]. Myocardial cell cultures grown to compare the lifespan and resistance of female vs male cells to injury could indeed provide confirmation to this hypothesis. Moreover, the relevance of such human results appears even greater in the light of the current search for myocardial progenitor or stem cells, able to mobilize to the heart and/or duplicate and replenish missing or fibrous myocardial regions. Indeed, it has been hypothesized that stem cells from female donors could more effectively duplicate and resist the multiple pro-apoptotic stimuli likely to be found in the host diseased heart.

Conclusions

Extensive epidemiologic, experimental and clinical evidence shows that unfavorable cardiac remodeling and heart failure are less common and less severe in women than in men. Several pathophysiologic mechanisms are probably involved in the transition from adaptive to unfavorable cardiac remodeling and may be responsible for such gender differences. In particular, myocardial apoptosis, which plays a central role in cardiac remodeling and failure, appears to be significantly increased in males in comparison to females in a wide range of clinical conditions, including early and late after acute myocardial infarction. However, the precise role of gender in the modulation of post-infarction myocardial apoptosis, the underlying intracellular mechanisms and their correlation with the remodeling processes still need to be thoroughly assessed.

The precise understanding of gender-related causes, mechanisms and potential modulators of ongoing post-infarction myocardiocyte apoptosis may indeed yield important pathophysiologic and therapeutic insights, potentially bringing clinically relevant benefits to both sexes.

References

1. Douglas PS. Coronary artery disease in women. In: Braunwald E, Zipes DP, Libby P, eds. Heart disease: a textbook of cardiovascular medicine. Philadelphia, PA: WB Saunders, 2001: 2038-51.
2. Mercuro G, Rosano GM. Coronary heart disease in women. Past gaps and current understanding. Ital Heart J 2003; 4: 505-7.
3. Heart disease and stroke statistics - 2004 update. American Heart Association. Available online at: http://www.aha.org (last accessed on 1 April 2004).
4. Fetters JK, Peterson ED, Shaw LJ, Newby LK, Califf RM. Sex-specific differences in coronary artery disease risk factors, evaluation, and treatment: have they been adequately evaluated? Am Heart J 1996; 131: 796-813.

5. Andreotti F, Conti E, Lanza G, Crea F. Sex, survival bias, and mortality following acute myocardial infarction. Ital Heart J 2003; 4: 508-10.
6. De Feo S, Opasich C. Comparison of the outcome in men and women with chronic heart failure. Ital Heart J 2003; 4: 511-3.
7. Presbitero P, Carcagnì A. Gender differences in the outcome of interventional cardiac procedures. Ital Heart J 2003; 4: 522-7.
8. Penco M, Fratini S, Romano S, Novo S. Gender differences in the outcome of noninvasive cardiovascular treatment. Ital Heart J 2003; 4: 514-7.
9. Modena MG, Nuzzo A, Rossi R. Gender differences in diagnostic procedures. Ital Heart J 2003; 4: 518-21.
10. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. N Engl J Med 1971; 285: 1441-6.
11. Schocken DD, Arrieta MI, Laeverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Cardiol 1992; 20: 301-6.
12. Felker GM, Shaw LK, O'Connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. J Am Coll Cardiol 2002; 39: 210-8.
13. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure. Results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). Circulation 2001; 103: 375-80.
14. Hellermann JP, Jacobsen SJ, Reeder GS, et al. Heart failure after myocardial infarction: prevalence of preserved left ventricular systolic function in the community. Am Heart J 2003; 145: 742-8.
15. Masoudi FA, Havranek EP, Smith G, et al. Gender, age, and heart failure with preserved left ventricular systolic function. J Am Coll Cardiol 2003; 41: 217-23.
16. Alter DA, Naylor CD, Austin PC, Tu JV. Biology or bias: practice patterns and long-term outcomes for men and women with acute myocardial infarction. J Am Coll Cardiol 2002; 39: 1909-16.
17. Cariou A, Himbert D, Golmard JL, et al. Sex-related differences in eligibility for reperfusion therapy and in-hospital outcome after acute myocardial infarction. Eur Heart J 1997; 18: 1583-9.
18. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM, for the National Registry of Myocardial Infarction 2 Participants. Sex-based differences in early mortality after myocardial infarction. N Engl J Med 1999; 341: 217-25.
19. Yap YG, Duong T, Bland M, et al. Is there a gender difference in the risk of arrhythmic death after acute myocardial infarction? An insight from contemporary survival studies. (abstr) J Am Coll Cardiol 2002; 39: 326B.
20. Becker RC, Hochman JS, Cannon CP, et al. Fatal cardiac rupture among patients treated with thrombolytic agents and adjunctive thrombin antagonists: observations from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction 9 Study. J Am Coll Cardiol 1999; 33: 479-87.
21. Woodfield SL, Lundergan CF, Reiner JS, et al. Gender and acute myocardial infarction: is there a different response to thrombolysis? J Am Coll Cardiol 1997; 29: 35-42.
22. MacIntyre K, Steward S, Capewell S, et al. Gender and survival: a population-based study of 201 114 men and women following a first acute myocardial infarction. J Am Coll Cardiol 2001; 38: 729-35.
23. Opasich C, Tavazzi L, Lucci D, et al. Comparison of one-year outcome in women versus men with chronic congestive heart failure. Am J Cardiol 2000; 86: 353-7.
24. Piepoli MF, Davos C, Francis DP, Coats AJ, for the ExTraMATCH Collaborative Group. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ 2004; 328: 189.
25. O'Farrel P, Murray J, Huston P, LeGrand C, Adamo K. Sex differences in cardiac rehabilitation. Can J Cardiol 2000; 16: 319-25.
26. Weinberg EO, Thienelt CD, Katz SE, et al. Gender differences in molecular remodeling in pressure overload hypertrophy. J Am Coll Cardiol 1999; 34: 264-73.
27. Gardner JD, Brower GL, Janicki JS. Gender differences in cardiac remodeling secondary to chronic volume overload. J Card Fail 2002; 8: 101-7.
28. Jain M, Liao R, Podesser BK, Ngoy S, Apstein CS, Eberli FR. Influence of gender on the response to hemodynamic overload following myocardial infarction. Am J Physiol 2002; 283: H2544-H2550.
29. Luchner A, Brockel U, Muscholl M, et al. Gender-specific differences of cardiac remodeling in subjects with left ventricular dysfunction: a population-based study. Cardiovasc Res 2002; 53: 720-7.
30. Carroll JD, Carroll EP, Feldman T, et al. Sex-associated differences in left ventricular function in aortic stenosis of the elderly. Circulation 1992; 86: 1099-107.
31. Camper-Kirby D, Welch S, Walker A, et al. Myocardial Akt activation and gender. Increased nuclear activity in females versus males. Circ Res 2001; 88: 1020-7.
32. Leri A, Malhotra A, Liew CC, Kajstura J, Anversa P. Telomerase activity in rat cardiac myocytes is age and gender dependent. J Mol Cell Cardiol 2000; 32: 385-90.
33. Gao XM, Dart AM, Percy E. Sex difference in cardiomyopathy phenotype in mice overexpressing beta-2 receptors in the heart. (abstr) J Am Coll Cardiol 2002; 39: 347B.
34. Crackower MA, Sarao R, Oudit GY, et al. Angiotensin-converting enzyme 2 is an essential regulator of heart function. Nature 2002; 417: 822-8.
35. Mendelson ME, Karas RH. The protective effects of estrogen on the cardiovascular system. N Engl J Med 1999; 340: 1801-11.
36. Smith PJ, Ornatsky O, Stewart DJ, et al. Effects of estrogen replacement on infarct size, cardiac remodeling, and the endothelin system after myocardial infarction in ovariectomized rats. Circulation 2000; 102: 2983-9.
37. van Eickels M, Patten RD, Aronovitz MJ, et al. 17-Beta-estradiol increases cardiac remodeling and mortality in mice with myocardial infarction. J Am Coll Cardiol 2003; 41: 2084-92.
38. Grohé C, Kajlert S, Löbbert K, Vetter H. Expression of oestrogen receptor α and β in rat heart: role of local oestrogen synthesis. J Endocrinol 1998; 156: R1-R7.
39. Gabel SA, Cross HR, Walker VR, et al. Gender effects of ischemia reperfusion injury: the role of estrogen receptor alpha and beta. (abstr) J Mol Cell Cardiol 2002; 34 (Suppl): A23.
40. Pelzer T, Schumann M, Neumann M, et al. 17Beta-estradiol prevents programmed cell death in cardiac myocytes. Biochem Biophys Res Commun 2000; 268: 192-200.
41. Wencker D, Chandra M, Nguyen K, et al. A mechanistic role for cardiac myocyte apoptosis in heart failure. J Clin Invest 2003; 111: 1497-504.
42. Abbate A, Biondi-Zoccai GGL, Baldi A. Pathophysiologic role of myocardial apoptosis in post-infarction left ventricular remodeling. J Cell Physiol 2002; 193: 145-53.
43. Abbate A, Biondi-Zoccai GGL, Bussani R, et al. Increased myocardial apoptosis in patients with unfavorable left ventricular remodeling and early symptomatic post-infarction heart failure. J Am Coll Cardiol 2003; 41: 753-60.
44. Mani K, Kitsis RN. Myocyte apoptosis: programming ventricular remodeling. J Am Coll Cardiol 2003; 41: 761-4.
45. Kocher AA, Schuster MD, Szabolcs MJ, et al. Neovascular-

ization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. Nat Med 2001; 7: 430-6.
46. Olivetti G, Quaini F, Sala R, et al. Acute myocardial infarction in humans is associated with activation of programmed myocyte cell death in the surviving portion of the heart. J Mol Cell Cardiol 1996; 28: 2005-16.
47. Baldi A, Abbate A, Bussani R, et al. Apoptosis and post-infarction left ventricular remodeling. J Mol Cell Cardiol 2002; 34: 165-74.
48. Olivetti G, Giordano G, Corradi D, et al. Gender differences and aging: effects on the human heart. J Am Coll Cardiol 1995; 26: 1068-79.
49. Leri A, Kajstura J, Li B, et al. Cardiomyocyte aging is gender-dependent: the local IGF-1-IGF-1R system. Heart Dis 2000; 2: 108-15.
50. Mallat Z, Fornes P, Costagliola R, et al. Age and gender effects on cardiomyocyte apoptosis in the normal human heart. J Gerontol A Biol Sci Med Sci 2001; 56: M719-M723.
51. Guerra S, Leri A, Wang X, et al. Myocyte death in the failing human heart is gender dependent. Circ Res 1999; 85: 856-66.
52. Biondi-Zoccai GGL, Abbate A, Bussani R, et al. Reduced post-infarction myocardial apoptosis in women: a clue to their different clinical course? Heart 2004, in press.
53. Biondi-Zoccai GGL, Abbate A, Bussani R, et al. Reduced post-infarction myocardial apoptosis in women: a clue to their different clinical course? (abstr) J Am Coll Cardiol 2003; 41: 381A.
54. Zhao X, Eghbali-Webb M. Gender-related differences in basal and hypoxia-induced activation of signal transduction pathways controlling cell cycle progression and apoptosis, in cardiac fibroblasts. Endocrine 2002; 18: 137-45.