

The Role of Biologic Sex in Anaphylactoid Contrast Reactions: An Important Consideration for Women of Reproductive Age and Undergoing Hormone Replacement Therapy

Jesse M. Klostranec, MD, PhD¹ • Taryn Rohringer, BS • Rachel Gerber, MD • Kieran J. Murphy, MD

The use of intravascular contrast agents is essential for maximizing diagnostic utility of routine medical imaging, improving lesion detection, and allowing for noninvasive assessment of vascular structures. Approximately half of the clinical annual 76 million CT and 34 million MRI examinations use intravascular iodinated contrast media (ICM) or a form of gadolinium-based contrast agent (GBCA), respectively (1). Adverse events because of administration of these contrast agents are rare but not infrequent given the large volume of examinations performed. From a clinical perspective, the most concerning subset of adverse events related to intravascular contrast administration are acute reactions with severe symptoms that resemble anaphylaxis and seem to disproportionately affect women of reproductive age (2,3). Although rare for GBCAs with a rate estimated at 0.52 per 10 000 administrations (and even lower for nonionic linear GBCAs) (4), such events were reported by the Japanese Committee on the Safety of Contrast Media to occur in 0.04% of examinations with ICM and can be fatal (estimated rate of fatal reactions to ICM administration is one fatality in 170 000 administrations) (1). With no previous sensitizing event occurring, these reactions are considered anaphylactoid because the overwhelming majority lack an immunoglobulin E (IgE) immune response (type I hypersensitivity), although a small number of such reactions are IgE positive at skin testing (1,5). Because of the severity of these reactions, a need exists for improved understanding of the associated pathophysiologic cause.

Well-known risk factors for acute adverse events following intravascular contrast administration include a history of previous reaction, other severe allergies or reactions to medications and/or food, asthma, atopy, cardiac or renal disease, or extremes of age (<5 years and >60 years) (6). However, it has also been noted that biologic sex appears to be a factor (7,8). This was first described by Lasser et al (2,9) following reassessment of data from a large multi-institutional trial that found increased incidence of reactions in women between the ages of 18 and 30 years. A later study of 5264 consecutive patients by Lang et al (3) also found a higher risk for reactions to ICM in women (odds ratio, 2.40) and much greater risk for anaphylactoid reactions to ICM in women, accounting for 21 of 22 (95%) severe reactions (odds ratio,

21.77). A biologic sex difference for the risk of contrast reaction may not be surprising considering the difference in the number of X chromosomes in men and women appears to have an effect on immune responses (10). The X chromosome contains approximately 1100 genes (about 5% of the human genome, with many related to immune function), whereas the Y chromosome has only approximately 100. Because of mosaic expression of the parental X chromosomes, greater genetic diversity exists in female immune cells, and although this may be advantageous regarding immunity against infection or cancer, drawbacks of increased autoimmunity and atopy in women are well documented (10,11). This difference in immunity related to biologic sex is also well demonstrated in data from the current coronavirus disease 2019 pandemic, with reports of case fatality rates in men 1.7 times of those in women (12).

Sex hormones appear to add further variability to the complex chromosomal, genomic, and epigenetic differences between the sexes that regulate immunity. Whereas androgens (eg, testosterone and dihydrotestosterone) and progesterone tend to suppress immune cell function, estrogen has been shown to enhance multiple immune responses (11). For example, a male predominance for allergic asthma, allergic rhinitis, and atopic dermatitis exists in childhood, but this switches to a female predominance after adolescence in the female reproductive period (13). Furthermore, variances in skin-prick test results have been demonstrated depending on the point in a woman's menstrual cycle, with an increased reaction to histamine most prominent on days 12–16, regardless of whether the patient was in the allergic or control group (14). Therefore, estrogens may enhance allergic reactivity in women around menstruation, pregnancy, and in those undergoing hormone replacement therapy (HRT). In fact, postmenopausal women undergoing HRT have a reported increased risk of adult-onset asthma and asthma exacerbations, whereas administration of an oral contraceptive pill and pregnancy are both associated with an increased risk of exacerbation of asthma symptoms (15–17). By extension, it appears reasonable to suspect estrogen may play an important role in anaphylactoid reactions to ICM.

Motivated by an increased incidence of anaphylaxis in premenopausal women from an Anaphylaxis Registry

From the Department of Medical Imaging, University of Toronto, Toronto, Canada; and Division of Neuroradiology, Toronto Western Hospital, University Health Network, 399 Bathurst St, Toronto, ON, Canada M5T 2S8. Received August 27, 2020; revision requested October 2; revision received December 4; accepted December 15. Address correspondence to K.J.M. (e-mail: kieran.murphy@uhn.ca).

Current address:

¹Department of Diagnostic and Interventional Neuroradiology, the Montreal Neurological Institute and Hospital, McGill University Health Center, Montreal, Canada.

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database, Hox et al (18) used a passive systemic anaphylaxis mouse model to test the role of estrogen in this process. They found that estradiol caused an upregulation of endothelial nitric oxide (NO) synthase (eNOS) in female mice and that this increased constitutive expression and enzymatic activity accounted for the observed higher incidence of passive systemic anaphylaxis in female mice. Importantly, a linear correlation was demonstrated between the serum estradiol levels and the severity and duration of anaphylaxis. The sex differences in passive systemic anaphylaxis were obliterated with the use of either the NO synthase inhibitor L-NG-nitroarginine methyl ester or an estrogen receptor blocker (fulvestrant), pointing to increased NO production

as the cause of passive systemic anaphylaxis. Female mice with ovariectomy also demonstrated slightly higher levels of eNOS than did male mice, although not with statistical significance, suggesting that sex differences in endothelial cell (EC) transcription profiles may also play a minor role. Because no significant differences were demonstrated in the serum levels of mast cell mediators histamine and mast cell protease 1 for the marked passive systemic anaphylaxis differences in ovariectomized and sham female mice, it was concluded that the effect of estrogen on anaphylaxis is subsequent to mast cell mediator release, corresponding to a marked NO-mediated increase in vascular permeability (18).

Rapid signaling drives eNOS activation (through phosphorylation and dimerization) and NO formation, with eNOS more densely positioned around myoendothelial junctions to facilitate localized NO diffusion between the endothelium and vascular smooth muscle cells in small arteries and arterioles (Figure) (19). Therefore, in addition to its beneficial increases in mitochondrial biogenesis and telomerase activity, NO serves as an important vasodilator that targets guanylyl cyclase to produce cyclic guanosine monophosphate to relax vascular smooth muscle cells. Elevation above basal eNOS-mediated NO production occurs in response to shear stress, hormones (such as estrogen), or autacoids (20). Although essential for ischemia-induced angiogenesis, it is known that an intrinsic sexual dimorphism exists in human ECs related to eNOS expression level and activity, demonstrating a stronger dependence for chemotaxis in female ECs, that serves essential roles in wound healing and angiogenic sprouting compared with male ECs (20). Furthermore, age-related changes in estrogen receptor expression levels are also known to reduce NO bioavailability (21). Because it appears that higher estrogen levels in premenopausal women correlate with increased basal eNOS

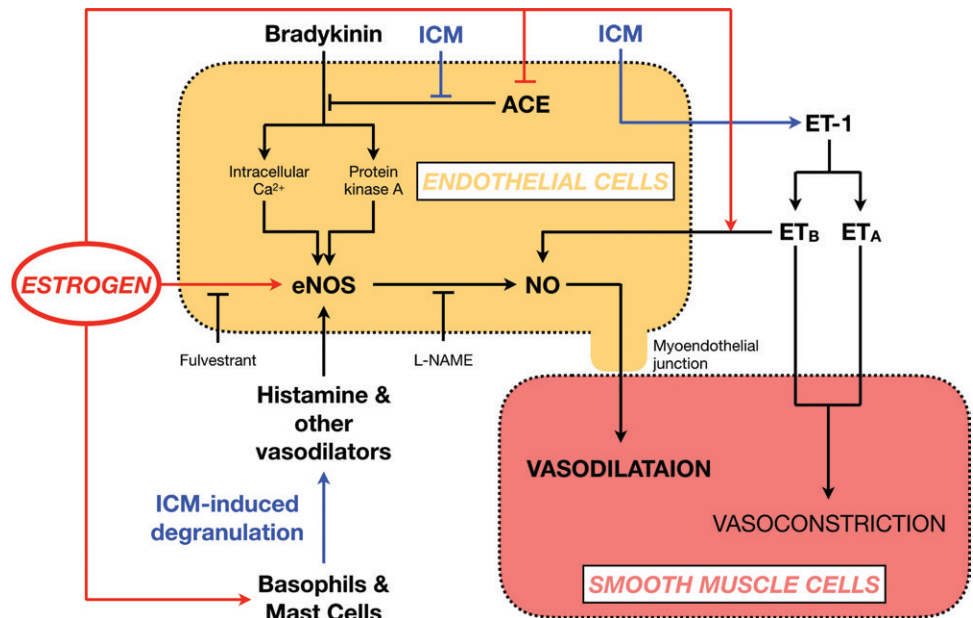


Figure Illustration of the interactions, to our knowledge, between estrogen and endothelial nitric oxide (NO) production that are suspected to have a role in the extensive vasodilation during anaphylactoid reactions. ACE = angiotensin converting enzyme, eNOS = endothelial NO synthase, ET-1 = endothelin-1, ICM = iodinated contrast media, L-NAME = L-NG-nitroarginine methyl ester.

expression, lower concentrations of vasodilation mediators to induce an anaphylactoid reaction may be required (Table) (22).

How does ICM administration trigger eNOS to produce NO at levels that cause life-threatening changes in vascular permeability? Instead of a sole molecular mechanism, it appears that NO production is a cumulative response to multiple inputs. With IgE mechanisms detected in only approximately 4% of severe reactions, effects of histamine and/or the kinin system are commonly cited (Figure) (23,24). Severe reactions have reported frequent mast cell degranulation, which results in the release of histamine and other vasodilating mediators (25). Multiple animal experiments have demonstrated upregulation of eNOS and increased NO production by histamine, which is preformed and stored in basophils and mast cells, although to our knowledge the mechanism by which ICM activates these cells remains unknown (23,26). Mast cell number and histamine levels have also been shown to correlate with estrogen levels and fluctuate with the menstrual cycle (27). Although high-quality studies are lacking, available evidence suggests at least some efficacy of administering antihistamines immediately before ICM administration to reduce the risk of an adverse reaction (28). Bradykinin, on the other hand, has a well-documented role in nonallergic angioedema and higher potency for anaphylaxis compared with histamine on a molar basis (29,30). As an extremely potent vasodilating substance, bradykinin increases intracellular Ca^{2+} levels that helps activate Ca^{2+} -sensitive eNOS while also activating protein kinase A to acutely increase NO production secondary to eNOS phosphorylation (30). Bradykinin is hydrolyzed by angiotensin-converting enzyme, which has been shown to be inhibited by ICM and may explain elevated plasma bradykinin levels that are known to exist after administration of ICM (29). Biologic sex may play a further role because angiotensin-converting enzyme

Significant Studies Demonstrating Biologic Sex Differences in Atopy and Nitric Oxide Production

Reference	Subjects	Major Findings
Lindgren et al (7)	500 consecutive patients undergoing intravenous cholegraphies	Contrast reaction rate for women in the fertile age period was 14.1%, whereas it was only 6.7% for nonfertile-age women.
Lasser et al (2)	6763 patients at multiple institutions undergoing CT with intravenous contrast administration	Pretreatment regimen with corticosteroid reduced incidence of all contrast reactions. A reassessment of the data showed women between the ages of 18 and 30 y demonstrated a significantly higher rate of contrast reactions, reactions requiring treatment, and "grade II" reactions.
Lang et al (3)	5191 consecutive patients administered iodinated contrast media for CT	Contrast reactions occurred in 1.39% of cases, with 70% occurring in women; 95% (21 of 22) of acute severe reactions occurred in women.
Power et al (8)	32 991 consecutive patients administered GBCA for MRI	Higher reaction rate seen in women, with all four moderate or severe reactions occurring in women.
Osman et al (13)	Reviewed population sample of 266 733 in Scotland from 1998–1999 and 6 836 063 in England and Wales from 1991–1995 for presentations of asthma, allergic rhinitis, and eczema	Allergic asthma, allergic rhinitis, and atopic dermatitis takes a female predominance at adolescence.
Kalogeromitros et al (14)	15 atopic menstruating women (mean age, 25.2 y) and 15 nonatopic menstruating healthy control participants (mean age, 24.7 y) were assessed with skin-prick tests during different days of their cycle	Greatest reactions to histamine occurred at days 12–16 of menstrual cycle, corresponding to peak estrogen levels, in both atopic and nonatopic groups.
Romieu et al (15)	57 664 women without asthma at menopause and undergoing HRT	569 incident cases of asthma were identified, demonstrating HRT is related to an increased risk of asthma onset.
Hox et al (18)	Developed and tested a passive anaphylaxis mouse model for the role of estrogen in the process	Estrogen was found to upregulate eNOS and NO production, with a linear relationship between estrogen serum level and duration of anaphylaxis.
Cattaneo et al (20)	In vitro and ex vivo experiments on human male and female ECs	Female ECs expressed higher eNOS mRNA and protein levels, associated with higher enzymatic activity and NO production.

Note.—EC = endothelial cell, eNOS = endothelial NO synthase, GBCA = gadolinium-based contrast agent, HRT = hormone replacement therapy, NO = nitric oxide.

levels are downregulated in the presence of estrogen and have been demonstrated to be elevated in female animals with ovariectomy and decreased with estrogen replacement (22,31).

One other less-expected potential trigger for increased NO production after administration of ICM may be through endothelin-1 (ET-1) signaling (Figure). ET-1 is a peptide produced by the endothelium that is, to our knowledge, the most potent vasoconstrictor known (22). Interestingly, ECs in vivo and in culture have been shown to release ET-1 in response to exposure to ICM (32). There are two subtypes of ET-1 receptors, ET_A and ET_B. Both are found on vascular smooth muscle cells with stimulation inducing vasoconstriction, whereas only ET_B is expressed by ECs, producing vasodilation by NO release (33). The latter appears to be influenced by estrogen, and greater expression of ET_B on ECs than vascular smooth muscle cells is seen in premenopausal women compared with age-matched men and EC ET_B expression attenuates in postmenopausal women (22,34). Furthermore, estradiol has been shown to reduce ET-1 levels in culture and HRT to reduce its level in plasma, whereas the lowest plasma levels of ET-1 are detected during the luteal phase of the menstrual cycle when estradiol and progesterone levels are elevated (22,35,36).

Thus, whereas ET-1 is considered a significant vasoconstrictor in men, multiple animal models suggest this vasoconstrictive tone is attenuated in women by physiologic concentrations of estrogen, favoring vasodilation (22). Thus, ET-1 changes related to ICM exposure may increase ET_B mediated vasodilatation and/or blunt the counteracting vasoconstrictive effects of ET-1, making an individual more sensitive to any other vasodilatory stimulus.

Despite this being an urgent clinical situation, to our knowledge little has changed in recent years regarding the understanding of the mechanisms of severe acute adverse reactions to intravascular contrast media (37). Expression of more than 6500 protein-encoding genes are different between men and women, and as we have tried to illustrate here, the resulting sexual dimorphisms that exist related to function of the endothelial and immune systems may have a significant role in explaining the differences in severe acute ICM reactions on the basis of biologic sex (20). We have briefly reviewed the current knowledge available to explain why the estrogen levels of reproductive-age women and of those undergoing HRT seem to put them at a significantly higher risk of these severe episodes. At our hospital, we screen patients with serum creatine levels for suitability

for imaging examinations with ICM. From our discussion, one might question whether serum estrogen levels in premenopausal women and women undergoing HRT should also be included. A prospective trial in collaboration with allergists and immunologists that records this information for menstruating women or women undergoing HRT (or perhaps more feasibly records the day of a woman's menstrual cycle or HRT dose) and determines the risk for acute severe contrast reactions would be helpful in confirming estrogen level as a significant risk factor, and might be of interest to funding sources such as the National Institute of Allergy and Infectious Diseases. Such improvements in our understanding of the consequences of these sex differences appear necessary to produce more effective screening, risk stratification, and precontrast administration protocols.

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