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translational science

Of mice and women: do sex-dependent responses to ischemia-reperfusion injury in rodents have implications for delayed graft function in humans?

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In rodent models, female sex has been shown to be protective against ischemia-reperfusion injury. A recent publication suggests that this sex-dependent response to injury may have clinical implications for delayed graft function after kidney transplantation.

Refers to: Aufhauser DD, Jr, Wang Z, Murken DR, et al. Improved renal ischemia tolerance in females influences kidney transplant outcomes. *J Clin Invest*. 2016;126:1968–1977.

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In small animal models, females display greater tolerance of ischemia-reperfusion injury (IRI) of multiple organs including the kidney.[1] Although a sex-dependent response to IRI is well established in animal models, the relevance to human health has been largely unexplored. A recent publication in the *Journal of Clinical Investigation*[2] provides preliminary evidence that sex-dependent differences in IRI may have clinical relevance in the setting of kidney transplantation.

Using a model of unilateral IRI with nephrectomy of the contralateral kidney, the investigators first confirmed previous observations that female C57BL/6 mice are protected from renal IRI, surviving up to 28 minutes of warm ischemia compared with only 15 minutes in male mice. After ovariectomy or orchiectomy, mice demonstrated an intermediate response, surviving up to 28 minutes of warm ischemia but with significant delays in renal recovery compared with hormonally intact females. When similar experiments were performed in estrogen receptor-α knockout mice, survival was significantly shorter than in wild-type females and closer to that previously observed in male mice. The investigators then examined the effect of exogenous estrogen on the response to IRI in the same surgical model. Female mice treated with low-dose estrogen 16 hours and 1 hour before warm ischemia had less severe injury than vehicle-treated female mice, as demonstrated by renal function and histologic fibrosis scores, whereas no benefit was observed in male mice. There was a nonsignificant trend toward reduced injury in orchiectomized males treated with estrogen before IRI and in females treated with estrogen after IRI.[2] Together, these experiments suggest that both testosterone and estrogen contribute to the observed differences in IRI response, that the estrogen receptor is required for the protective effect in females, and that supplementation estrogen may be protective in females when IRI can be anticipated.[2]

The more novel contribution of the current study included a series of kidney transplantation experiments seeking to distinguish between the effects of the hormonal milieu and the intrinsic effects on the kidney itself

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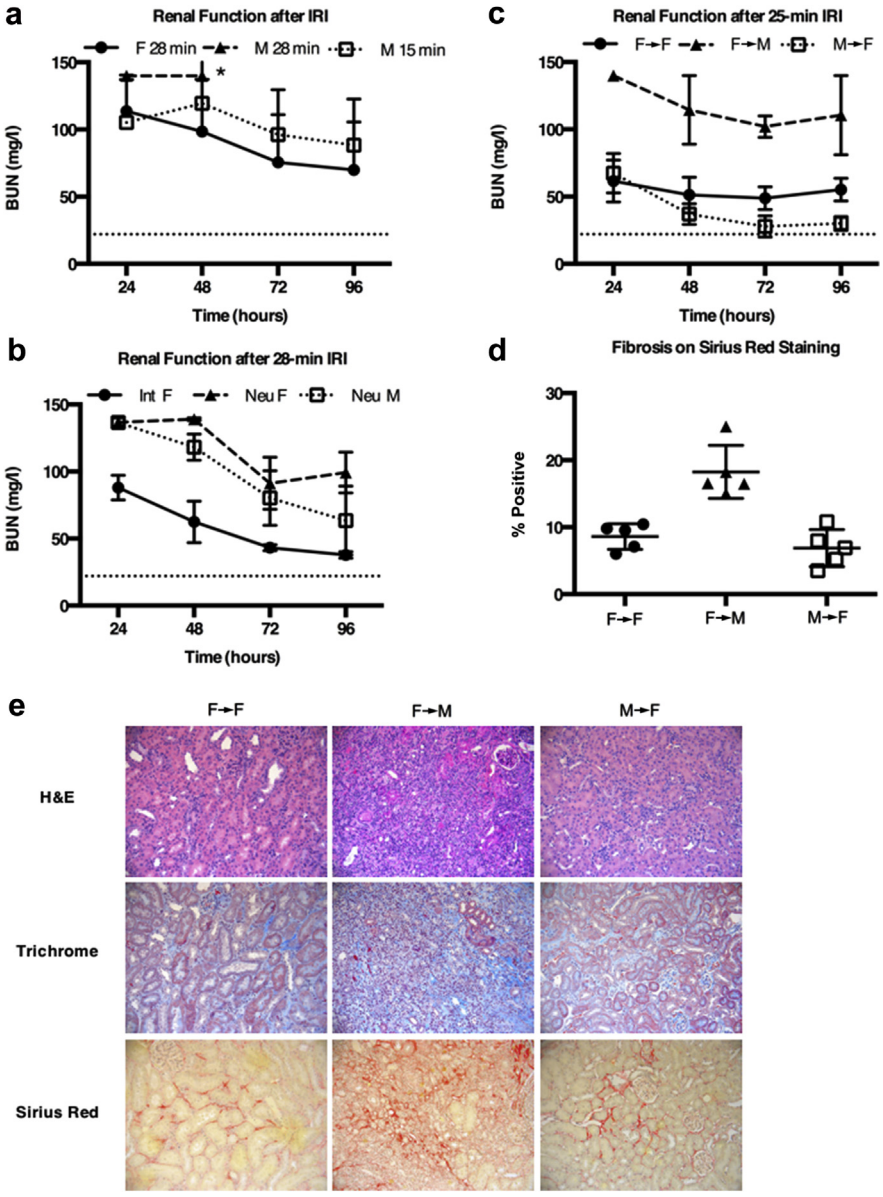

Figure 1 | Female hormonal environment protects against renal ischemia reperfusion injury (IRI). (**a**) Blood urea nitrogen (BUN) measurements after 28 minutes of renal IRI in female mice (F 28 min; $n = 10$) showed renal injury equivalent to that in male mice after 15 minutes of renal IRI (M 15 min; $n = 11$; $P = 0.36$, by 2-way analysis of variance [ANOVA]); 28-minute IRI was unsurvivable in male mice (M 28 min, *$n = 4$); dashed line shows the baseline BUN level. (**b**) Neutered female mice (Neu F; $n = 5$) had impaired renal function after warm IRI compared with that seen in intact female mice (Int F; $n = 5$; $P < 0.01$, by 2-way ANOVA). Neutered male mice (Neu M; $n = 5$) tolerated IRI with impairment similar to that in neutered females, but worse function than in intact females ($P < 0.01$, by 2-way ANOVA). (**c**) Female kidneys transplanted into female recipients (F→F; $n = 5$) and male kidneys transplanted into female recipients (M→F; $n = 5$) had similar impairment of renal function when subjected to 25 minutes of warm IRI. Female kidneys transplanted into male recipients (F→M; $n = 5$) had decreased survival (2 of 5), with significantly higher BUN levels compared with those of either of the other 2 groups ($P < 0.0001$, by 2-way ANOVA). (**d**) The F→M transplanted kidneys had significantly more fibrosis on Sirius red staining at 28 days than did the transplanted kidneys in either of the other 2 groups ($P < 0.001$, by 1-way ANOVA). (**e**) Hematoxylin and eosin (H&E), trichrome, and Sirius red staining (original magnification, ×20) showed increased fibrosis in the F→M cohort compared with that observed in the F→F and M→F cohorts. Error bars indicate the mean ± SEM. Reproduced with permission from Aufhauser DD Jr, Wang Z, Murken DR, et al. Improved renal ischemia tolerance in females influences kidney transplant outcomes. *J Clin Invest*. 2016;126:1968–1977.

(Figure 1). In these experiments, native nephrectomy was performed 5 days after syngeneic kidney transplantation so that renal function reflected only the transplanted kidney. In the first set of experiments, transplantations were performed with minimal cold ischemia time, and mice were allowed to recover for 4 weeks before being subjected to warm ischemia in order to minimize the effects of IRI related to the transplantation procedure.