Hypertensive Living Kidney Donor Candidates: What's the Risk?

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Living kidney donation is endorsed by the global kidney and transplant community. Living donor kidney transplantation is usually the best treatment option for patients with end-stage kidney failure (ESKF). Paramount, living kidney donors do not themselves gain (medically) from the donor nephrectomy. Therefore, perioperative and long-term risks of kidney donation need to be kept low to allow this highly valued procedure to continue.

To minimize risks, living kidney donors are, in principle, required to be healthy at the time of donation. Stringent health requirements for donors yield low perioperative risks. There are obvious but small risks (a few percentage points) of bleeding and infection. Perioperative mortality is rare. According to large registries, 1 in 3000 (0.03%) donor nephrectomies proves fatal.[1] This risk is comparable to the 3-year risk of a fatal motor vehicle accident in the United States (11.5/100,000 population in 2019, i.e., 0.01% per year).[2] Given the improved health for the recipient, these risks are regarded as acceptable but need to be communicated to and understood by potential kidney donors in order to achieve informed consent.

There are more debate and discrepant studies regarding the long-term risks after kidney donation. During the last decade, several studies in kidney donors have found increased risks of hypertension, pre-eclampsia, cardiovascular disease, ESKF, and mortality.[3–5] Studies on ESKF and mortality used control groups which were selected to be healthy to allow for a valid comparison, because donors are also selected to be healthy at the time of donation. Interestingly, several of the outcomes did not differ between groups before a considerable time had passed since donation, i.e., about 10 to 15 years for ESKF and mortality.[3] Yet another unresolved issue is whether hereditary factors (rather than the donor nephrectomy per se) may underlie the increased risk of ESKF and mortality in donors, because many are closely related to their recipients.[3]

The shortage of deceased donor kidneys has spurred several initiatives to expand living donor kidney transplantation, including kidney paired donation and lifting health requirements for donors. There is a tendency to accept more obese and hypertensive donors, reflecting the prevalence of these conditions in the general population. Concerns still exist about the outcomes of such practice.

In this issue, Ibrahim *et al.*[6] provide a timely report on outcomes in hypertensive donors compared with normotensive donors. This is a commendable effort, because there are few articles previously published on this subject. The authors used publicly available data from The Renal and Lung Living Donor Evaluation (RELIVE) Study, representing 3 U.S. transplant centers: The University of Minnesota, Mayo Clinic-Rochester, and the University of Alabama-Birmingham. Nephrectomies were performed during years 1963 to 2007, and outcomes until 2010 to 2012 ascertained retrospectively by study personnel contacting the donors, their transplant centers, or their respective kidney recipients. Among 8721 donors, 904 (10.4%) had predonation hypertension, defined as blood pressure (BP) ≥140/90 mm Hg or on treatment. In a supplementary analysis, 2369 (27.2%) of donors were defined as hypertensive by a lower threshold (BP ≥130/80 mm Hg or on treatment). Overall, median age at donation was 39 years, 56% were women, and 85% were non-Hispanic white. The hypertensive group was older and contained more males.

After a mean follow-up of 17.6 years in nonhypertensive donors and 14.3 years in hypertensive donors, mortality occurred in 422

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(4.8%), cardiovascular disease in 1118 (12.8%), diabetes in 576 (7.2%), ESKF in 44 (0.5%), and a combined endpoint of ESKF or estimated glomerular filtration rate <30 ml/min/1.73 m^2 in 86 (1.0%), with no significant difference between the hypertensive (n = 904) and normotensive groups in unadjusted or multivariable adjusted Cox regression models. However, after accounting for approximately 5% missing values by multiple imputation, hypertensive donors were significantly more likely to experience cardiovascular disease (adjusted hazard ratio [HR] 1.34 [95% confidence interval {CI} 1.05–1.51]; $P = 0.02$). Also, in the supplementary analysis using the lower BP threshold for hypertension

(BP ≥130/80 mm Hg or on treatment), the hypertensive donors (n = 2369) experienced adverse outcomes with increased occurrence of diabetes (adjusted HR 1.41 [95% CI 1.08–1.83]; $P = 0.01$) and cardiovascular disease (adjusted HR 1.36 [95% CI 1.15–1.61]; $P < 0.001$), and a trend for increased mortality (adjusted HR 1.29 [95% CI 1.0–1.67]; $P = 0.051$). The risk of ESKF was not increased. These risks may be underestimated, because the authors included BP at evaluation among the adjustment variables, which is collinear with being hypertensive. Moreover, in absolute figures as shown above, ESKF is vastly outnumbered (by order of magnitude) by cardiovascular events and mortality, these two being the primary concern for

hypertensive donors. Some uncertainty exists when applying these risk estimates to current donor candidates, because in the present era there is less cardiovascular disease and more diabetes. Nevertheless, the strength of association between hypertension and cardiovascular outcomes reported by Ibrahim *et al.*[6] is of a similar magnitude as found in the general population.[7]

In their conclusion, Ibrahim *et al.*[6] focus on the lack of increased risk of ESKF and advocate for allowing hypertensive persons to donate if subtle renal disease is ruled out and the candidate is not at a magnified risk of cardiovascular disease from other risk factors than hypertension. We partially agree with this conclusion.

First, this study does not show whether kidney donation in a hypertensive person yields worse outcomes than deferring kidney donation, because there is no control group of hypertensive persons that did not donate. Second, if hypertension is aggravated by kidney donation, free lifelong follow-up and free treatment should be mandatory. That being said, many countries already have free lifelong follow-up of all donors. Finally, informed consent becomes more problematic as we incorporate more uncertainties into the evaluation process. Long-term risks for hypertensive young persons are particularly problematic because current studies and prediction models typically span 5 to 20 years of follow-up and not the remaining lifespan.[8] It is difficult both for the responsible physician and the potential donor to fully consider such uncertainties, although it is important that this is reflected in the information given.

The take-home message is in our opinion to assess total and lifelong cardiovascular risk more than

looking at the separate risk factors. Some of this information may be available to the responsible physician, such as demographic data, family history, socioeconomic factors, race, and age, although we acknowledge that looking into the future is not a simple task.[8] We suggest that one considers hypertension in a donor in relation to what would be normal in relation to age and gender. Uncomplicated hypertension in a 70-year-old potential donor, one without end-organ damage or other comorbid disorders and easily controlled with 1 antihypertensive drug, is quite common and unlikely to manifest as significant cardiovascular or renal disease. This is different in a 30-year-old potential donor, in which isolated hypertension is both rare and strongly indicative of future health problems, whether related to hereditary factors or lifestyle. Although Ibrahim *et al.*[6] do not make a clear stand on age limits for potential donors with hypertension, they suggest that a limit of 50 years of age may be reasonable. We support the concept of such a lower age limit for considering hypertensive donors. The report by Ibrahim *et al.*[6] is a step in the right direction to quantify the risk of using hypertensive donors.

DISCLOSURE

The authors declare no conflicts of interest.

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