Donors at risk: hypertension

SUGGESTIONS FOR CLINICAL CARE

- Potential living kidney donors should have their blood pressure (BP) measured on at least three occasions with a level less than 140/90 mmHg on all three occasions.
- If one or more office BP measurements are elevated, white-coat hypertension may be excluded by:
  - 12 home BP measurements with an average less than 135/85 mmHg or
  - 24 h ambulatory blood pressure measurement (ABPM) with an average less than 135/85 mmHg.
- An elevated BP on the above definitions is a relative contraindication to donation.
- Donors with:
  - evidence of end-organ damage related to hypertension (e.g. retinopathy, left ventricular hypertrophy, proteinuria), or
  - poorly controlled BP (e.g. requiring more than two medications or BP still elevated), or
  - other cardiovascular risk factors (e.g. elevated cholesterol, overweight, smoker, family history of cardiovascular disease) should not be considered for donation.

IMPLEMENTATION AND AUDIT

Short- and long-term live donor outcomes need to be closely monitored.

BACKGROUND

The aim of this guideline is to review the available literature in relation to live donor effects on BP and in the setting of pre-existing hypertension in the living donor. In particular, the following issues need to be considered:

(i) the effect of unilateral nephrectomy on BP in healthy, normotensive individuals, and
(ii) the long-term risks of donating a kidney if the donor has pre-existing hypertension.

Hypertension is a common disorder that is often found incidentally on routine medical examination. In many individuals, it has often been present for several years before it is eventually diagnosed. Even when considering a clearly normotensive individual, one must still consider the lifetime risk of developing hypertension in that individual. An additional factor to consider is that BP is known to rise with ageing.

The definition of hypertension has changed over time with the acceptable ‘treatable limits’ gradually falling over the past few decades. In addition, it is now accepted that the relationship between BP and cardiovascular risk does not have an absolute cut-off. The risk is continuous and is apparent in the normal range of BP (i.e. subjects with a higher normal BP have an increased cardiovascular risk compared with those with a lower normal BP. As an example, the cardiovascular risk is higher for a subject with a normal BP of 135/80 mmHg, when compared with an age- and gender-matched individual with a BP of 115/70 mmHg).

Individuals with hypertension or on antihypertensive therapy have been commonly excluded as kidney donors in the past. As a result, there is relatively little information available regarding the effects of donation on the long-term outcome in this group of live donors. At the present time due to a lack of appropriate data, it is difficult to clearly present conclusive information regarding the long-term effects of kidney donation in hypertensive individuals.

In practice, it is generally accepted that kidney donation is contraindicated in those with hypertensive end-organ damage, poorly controlled hypertension and hypertension that requires multiple medications to achieve adequate control. Many units accept kidney donors with well-controlled hypertension and without any evidence of end-organ damage but other factors such as the donor’s age and other medical factors are usually considered simultaneously. On the basis that uninephrectomy may increase BP some units choose to completely exclude hypertensive individuals even when their BP is well controlled on minimal medication. This would be particularly the case in younger donors who face their individual risks for a longer time after they donate.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text
words for living donor, and combined with MeSH terms and text words for hypertension. The search was carried out in Medline (1950–July Week 3, 2008). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline. Date of searches: 24 July 2008.

WHAT IS THE EVIDENCE?

Definition of hypertension

Assessment of living donors’ BP should consider the long-term cardiovascular risk and the presence of hypertension as a surrogate marker of underlying renal disease. The definition of hypertension and how BP should be measured requires some consideration. There is a well-established relationship between cardiovascular risk and degree of hypertension, however, the threshold for concern has been progressively lowered in more recent years. The definition of ‘hypertension’ as a threshold of measurement has been generally considered to be 140/90 mmHg, however, the most recent Joint National Committee now defines increased cardiovascular risk for individuals previously considered to be in the ‘normal’ range, and define a group of patients as ‘pre-hypertension’ with BP readings 120–140 systolic/80–90 diastolic. The implication of this redefinition of risk is that these patients previously considered to be in the normal range has not been evaluated for living donors. The method of BP measurement is an additional variable that needs further consideration. Assessment of live donors should include serial manual BP measurements on at least three separate outpatient visits as a minimum evaluation. The majority of studies evaluating BP measurement in the general population relating measurement to cardiovascular risk and morbidity have relied on manual measurement. The role of ABPM continues to be evaluated and has been shown to correlate with end-organ damage and predict cardiovascular risk better than manual BP measurement in some studies. If elevated manual BP is detected, then it may be worthwhile performing home self-BP measurements or ABPM, since 10–20% of patients with elevated manual measurements have normal BP by ABPM. A normal BP on home BP measurements or ABPM is an average of less than 135/85 mmHg.

Hypertensive potential living kidney donors

If hypertension is detected evidence of end-organ disease should be excluded by echocardiogram and ophthalmology assessment. Patients with evidence of end-organ damage should not be considered as donors, including potential donors with poorly controlled BP or those taking multiple antihypertensives.

In addition to detecting patients with ‘white-coat’ hypertension, ABPM may also improve the detection of hypertension. Ozdemir et al. studied renal donors and demonstrated that ABPM was more sensitive at detecting hypertensive patients than manual BP. Textor et al. also reported that ABPM is useful in the diagnosis of hypertension in renal donors, particularly elderly. Although the use of ABPM may provide valuable clinical information in selected potential donors, the value of routinely using ABPM in the assessment of donors requires further study.

The effect of donor nephrectomy on BP in a healthy donor

A further issue relates to whether or not nephrectomy increases the risk of developing hypertension in the long term. An increase in BP is commonly observed following nephrectomy, however, an increase in BP into the hypertensive range in previously normotensive individuals, remains to be determined. Studies examining this possibility are varied and have often used different control groups. Most commonly, the general population is used, and this may not be the most appropriate group to compare with healthy donors.

A number of studies report an incidence of hypertension following nephrectomy ranging from 9% to 48%. It is important to note that the definition of hypertension varies between these studies. Additionally, there are no studies that compare age- and gender-matched individuals in a prospective manner for individuals who either undergo nephrectomy or are followed without a nephrectomy.

Torres et al. followed patients post-nephrectomy for 10 years and defined hypertension as a systolic/diastolic BP of ≥160/95 mmHg. Ten of 66 patients (15%) who were previously normotensive became hypertensive and 9/24 (38%) of patients who had borderline hypertension developed hypertension according to the study definition. Clearly, the level of BP used to define hypertension here, is much higher than is generally used now and the relevance of the data from this study remains unclear.

Another study of 250 patients followed long-term for up to 10 years or more, demonstrated that ‘borderline hypertension’ (defined as 150–159/90–94 mmHg) developed in 8.8% and definite hypertension (160/95 mmHg or greater) developed in 5.6% of patients. The investigators compared the incidence of hypertension with the general population and concluded that this was lower than that seen in age-matched individuals.

Some small studies comparing BP in donors to control groups have suggested an increase in the risk of developing hypertension. However, most of the larger studies have not confirmed this. Goldfarb et al. studied 70 donors followed for a mean time of 25 years and found no increase in the risk of developing hypertension compared with age-matched individuals. Two larger studies, one of 402 donors with a mean follow-up of 12 years and another of 733 donors with a follow-up of up to 30 years or more, showed that the age-matched incidence of hypertension was not increased. Grossman et al. followed 152 donors with a mean time after uninephrectomy of 11 ± 7 (range: 1–28) years with a 93% retrieval rate. BP increased from 125 ± 15/79 ± 11 to 134 ± 19/81 ± 9 mmHg (P < 0.01) but remained in the normotensive range.
A large meta-analysis by Kasiske et al. of the long-term effects of reduced renal mass in humans examined mostly nephrectomy for renal donation, however, the group of patients was not uniform. The analysis examined 48 studies with 3124 patients and 1703 controls. Nephrectomy did not affect the incidence of hypertension, but an increase in systolic BP (2.4 mmHg, \( P > 0.05 \)) was observed, which increased further with follow up (1.1 mmHg/decade). Diastolic BP increased after nephrectomy (3.1 mmHg), but this increment did not change with duration of follow up.\(^{26}\)

Another large meta-analysis by Boudville et al.\(^{27}\) examined results from 48 studies with a total of 5145 donors (Fig. 1). They concluded that kidney donors had an increase in BP of approximately 5 mmHg systolic and 4 mmHg diastolic, above that expected with normal ageing, within 5–10 years of donation.

In the general population, every 10 mmHg increase in systolic BP and 5 mmHg increase in diastolic BP is associated with a 1.5-fold increase in mortality from both ischaemic heart disease and stroke.\(^{28}\)

Boudville et al.\(^{27}\) also reviewed the risk of developing hypertension in donors. Six studies were assessed (total of 249 donors comparing results against 161 control participants), however, results could not be pooled due to heterogeneity in the groups. Only one of the six studies (Watnick et al.\(^{29}\)) showed an increase in the risk of developing hypertension (relative risk: 1.9 (confidence interval: 1.5–3.5)). All others showed no difference. It must be noted that none of these studies were adequately powered to detect a meaningful difference between the study and the control groups (less than 80% chance of detecting a 1.5-fold increase in the risk of hypertension). The donor population in each individual study ranged from 15 to 50 patients whereas the control population ranged from 10 to 50 patients.

In summary, there is no conclusive evidence that kidney donation increases the risk of developing hypertension in normal individuals. The studies examining this, however, are very limited. Studies do show that kidney donation is associated with a small increase in BP within the normal range. Since reduced glomerular filtration rate (GFR) and hypertension are both important cardiovascular risk factors, it is very important to explain this potential added risk and also aggressively treat other cardiovascular risk factors such as smoking, hyperlipidaemia, obesity, metabolic syndrome and diabetes during follow up.

The effect of donor nephrectomy on donors with pre-donation hypertension

The presence of established hypertension in potential live kidney donors has been considered to be a contraindication to proceeding with donation. Conclusive recommendations regarding the routine use of hypertensive donors cannot be made at this stage since only short-term cohort studies have been reported. Textor et al.\(^{29}\) showed that 58 donors with normal renal function and controlled hypertension on 1–2 medications showed no increased risk of renal deterioration, microalbuminuria or poor BP control at 12 months. A follow-up study by the same investigators examined 148 living kidney donors before and 6–12 months after nephrectomy.\(^{1}\) Patients who were normotensive donors had no change in awake ABPM results. Of the 148 live donors, 24 were hypertensive (ABPM > 135/85 mmHg and clinic BP > 140/90 mmHg) before donation. The group concluded that patients with moderate, essential hypertension and normal kidney function have no adverse outcomes with respect to BP, renal function or urinary protein excretion in the first year after living kidney donation.

Young et al.\(^{20}\) performed a systematic review and meta-analysis and identified six studies on 125 hypertensive donors (Fig. 2).\(^{20}\) A number of methodological issues restrict the external validity of all of these studies. Follow up was for a median of 2.6 years, with two having a mean follow up of over 5 years. One study described a 14 \(\mu\)mol/L greater rise in serum creatinine in hypertensive donors compared with donors who were normotensive pre-donation. Two studies described conflicting results on the change in renal function using radioisotope or inulin GFR between 62 hypertensive donors and 27 normotensive donors. One study demonstrated that BP in hypertensive donors at 1 year decreased by 4 mmHg diastolic compared with normotensive donors. An additional study found that mean arterial BP following donation decreased more often in hypertensive donors.

**SUMMARY OF THE EVIDENCE**

Please refer to Table 1 – Characteristics of included studies (Appendices).

There is a lack of prospective controlled long-term data regarding the effects of nephrectomy in both normal and hypertensive donors. More precise information is required and this would ideally be collected prospectively using a live donor registry.

On the basis of limited studies, nephrectomy appears to lead to a small increase in BP but there is no evidence of an increased risk of developing hypertension. However, to better assess whether there is an alteration in the risk of developing hypertension, it is acknowledged that prospective studies of age- and sex-matched individuals with and without nephrectomy would need to be performed.

The recommendation to exclude from donation individuals with poorly controlled hypertension or with known hypertensive end-organ damage (e.g. retinopathy, left ventricular hypertrophy, stroke, proteinuria and renal impairment) is based on the known natural history of these disorders. No study has been performed comparing the outcome in these subjects who donate, compared with those who do not.

**WHAT DO THE OTHER GUIDELINES SAY?**

**British Transplant Society/British Renal Association:**

An extensive, 100-page document has been produced outlining similar issues to those discussed here.\(^{31}\) The full version of these British Live Donor Guidelines is available.
at: http://www.bts.org.uk/transplantation/standards-and-guidelines/

– Prospective donors should not be precluded from further evaluation if their office (casual) BP recordings are below 140/90 mmHg.

– Evidence of hypertensive end-organ damage is an absolute contraindication to kidney donation.

– If a prospective donor is on treatment for hypertension it may still be reasonable to consider proceeding if their BP is well controlled (less than 140/85 mmHg). They should be warned of the possibility that nephrectomy may increase their BP and subsequent cardiovascular risk and appropriate follow up should be arranged.

– Smoking, obesity and/or raised cholesterol in the context of hypertension place the donor at additional risk.

The Canadian Council for Donation and Transplantation:

A short manuscript outlining similar issues to those discussed here.32

Hypertension has been considered to be a contraindication in potential renal transplant donors. However, the precise risk to donors who have borderline elevation in BP (BP) and those with a family history of hypertension has not been conclusively determined.

The following consensus guidelines regarding hypertensive donors were adopted:

– Patients with a BP of 140/90 by ABPM are generally not acceptable as donors.

– BP should preferably be measured by ABPM, particularly among older donors (50 years) and/or those with high office BP readings.

– Some patients with easily controlled hypertension who meet other defined criteria (e.g. 50 years of age, GFR 80 mL/min and urinary albumin excretion < 30 mg/day) may represent a low-risk group for development of kidney disease after donation and may be acceptable as kidney donors.

– Donors with hypertension should be regularly followed by a physician.

European Renal Association-European Dialysis and Transplant Association:

Exclusion criteria include: ‘Reduced GFR (in comparison to normal range for age), proteinuria of >300 mg/day, microhematuria (except when an urologic evaluation and a possible kidney biopsy are normal),...or hypertension without good control’.13

The Canadian Council for Donation and Transplantation:9

It would appear that BP increases by ~5 mmHg after donating a kidney above the natural increase which occurs with normal aging. Most studies have not suggested an increased rate of hypertension following donation. To date no study using appropriate controls has examined whether donating a kidney increases the risk of premature death or cardiovascular disease over the long-term. This concern has been raised due to the observation that renal insufficiency is an independent risk factor for cardiovascular disease in the general population.

Not unexpectedly, there is considerable variability in practice particularly when it comes to accepting a potential living donor with hypertension or mildly abnormal renal function. In the case scenario involving a 50-year-old male with well-controlled hypertension on a single antihypertensive agent, 5 of 14 centres responded that they would never accept such an individual as a kidney donor. However, other centres would rarely (n = 2), sometimes (n = 5) and usually (n = 2) accept this individual as a living kidney donor.

Reference is also made to recommendations from the Amsterdam Forum, the British Renal Association and the European Renal Association-European Dialysis and Transplant Association.

SUGGESTIONS FOR FUTURE RESEARCH

1. Further prospective studies with appropriate control groups are required in order to determine whether nephrectomy in normotensive individuals increases the long-term risk of developing hypertension.

2. Further studies are needed to confirm long-term safety for potential donors with existing hypertension. These patients should form part of a study group or registry.

CONFLICTS OF INTEREST

Frank Lerino has received Educational Grants and fees for attendance at Conferences/Transplant Symposia from Wyeth, Roche, Janssen-Cilag and Novartis. He has also received an Unrestricted Research Grant from Roche and Novartis, has been a member of the medical advisory boards for Roche and Novartis and a member of the Drug Trial Safety Monitoring Board for Novartis. John Kanellis and Neil Boudville has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

REFERENCES


## APPENDICES

### Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Study methods</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boudville et al.</td>
<td>27</td>
<td>Meta-analysis, data sources included Medline, Embase, Science Citation Index</td>
<td>48 studies included 5145 donors.</td>
<td>Kidney donors may have 5 mmHg increase in BP 5–10 years after donation over anticipated normal aging.</td>
</tr>
<tr>
<td>Dunn et al. (1986)</td>
<td>314</td>
<td>Prospective follow-up data, 1970–1984</td>
<td>Major late complications were seen in 50 (20.0%) of 250 patients followed for 6 to 175 months (mean 53.1 months). These included definite hypertension (5.6%).</td>
<td>While the risk of hypertension appears to increase as the interval from donation increases, no cases of renal failure after donation were observed.</td>
</tr>
<tr>
<td>Goldfarb et al. (2001)</td>
<td>70</td>
<td>Follow-up data, 1963–1975</td>
<td>Of 48 studies included, 5145 donors. Kidney donors may have 5 mmHg increase in BP 5–10 years after donation over anticipated normal aging.</td>
<td>No gender differences were noted in BP.</td>
</tr>
<tr>
<td>Kasinke et al. (1995)</td>
<td>–</td>
<td>Meta-analysis</td>
<td>48 studies included 3124 patients and 1703 controls; unilateral nephrectomy decreased GFR but improved with each 10 years follow up. Patient with single kidneys had small progressive increase in proteinuria, but negligible after nephrectomy for trauma or kidney donation.</td>
<td>In normal individuals, unilateral nephrectomy does not cause progressive kidney function but may be associated with small increase in BP.</td>
</tr>
<tr>
<td>Ramcharan et al. (2002)</td>
<td>464</td>
<td>Follow-up data, 1963–1979</td>
<td>The rate of proteinuria and hypertension was similar to the age-matched general population.</td>
<td>Most kidney donors have normal renal function 20–37 years post donation. However, some do develop renal dysfunction and some develop renal failure.</td>
</tr>
<tr>
<td>Textor et al. (2004)</td>
<td>148</td>
<td>Prospective follow up before and 6–12 months after nephrectomy</td>
<td>Normotensive donors had no change in awake ABPM pressure, in hypertensive donors BP decreased with therapy.</td>
<td>White participants with moderate, essential hypertension and normal kidney function have no adverse effects (BP, GFR, urinary protein) during the first year after donation.</td>
</tr>
<tr>
<td>Torres et al. (1987)</td>
<td>99 living related kidney donors, 50 recipients</td>
<td>Follow-up data</td>
<td>Borderline and definite hypertension were present in 4.0% and 4.0% of donors prior to donation, in 14.4% and 21.1% of donors at follow up, and in 2.0% and 18.0% of the 50 recipients at follow up. Age, relative weight and MAP prior to donation were the key variables in predicting the follow-up ranked MAP of the donors. CPAH prior to donation was inversely correlated with the age of the donors and, indirectly, with the follow-up MAP. Donor CPAH prior to donation was significantly correlated with the renal allograft function of the recipients but not with the recipient ranked MAP or follow up. No correlation of the ranked MAP or BP outcome categories between donors and recipients was found.</td>
<td>Donation of one kidney can accelerate the development of hypertension in those donors with predisposition to develop hypertension. The predisposition of donors to develop hypertension and their age, within the range observed in the study, do not significantly influence the long-term BP of the recipients.</td>
</tr>
<tr>
<td>Williams et al. (1986)</td>
<td>38</td>
<td>Evaluation of renal function in donors and their siblings</td>
<td>No statistically significant difference was found between the prevalence of hypertension in donors and siblings.</td>
<td>With the exception of mild proteinuria of unknown clinical significance, unilateral nephrectomy is not associated with adverse effects on kidney function.</td>
</tr>
</tbody>
</table>

ABPM, ambulatory blood pressure measurement; BP, blood pressure; CPAH, clearance of para-amino hippurate; GFR, glomerular filtration rate; MAP, mean arterial pressure; SBP, systolic blood pressure.
Donors, post-donation

<table>
<thead>
<tr>
<th>Source</th>
<th>Years after donation, mean (range)*</th>
<th>Systolic blood pressure, mmHg N mean (sd) §</th>
<th>Use of anti-hypertensive medication(s), %</th>
<th>Controls</th>
</tr>
</thead>
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<tr>
<td>Najarian et al^50</td>
<td>8(1–19)</td>
<td>57 134 (15)</td>
<td>32</td>
<td>50 130 (21) 44</td>
</tr>
<tr>
<td>Undurraga et al^53</td>
<td>11(1–21)</td>
<td>30 125 (18)</td>
<td>…</td>
<td>30 118 (13) …</td>
</tr>
<tr>
<td>Talseth et al^54</td>
<td>11(10–12)</td>
<td>32 140 (23)</td>
<td>10</td>
<td>32 132 (29) …</td>
</tr>
<tr>
<td>Williams et al^57</td>
<td>13(10–18)</td>
<td>38 136 (25)</td>
<td>‡</td>
<td>16 129 (16) ‡</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td>157 133 (6)</td>
<td></td>
<td></td>
<td>128 126 (8)</td>
</tr>
</tbody>
</table>

Fig. 1 Meta-analysis of controlled studies of systolic blood pressure and diastolic blood pressure at least 5 years after kidney donation. The size of each square is inversely proportional to the variability of the study estimate. *Studies are arranged by the average number of years after donation. §A summary of various methods to assess blood pressure are presented in the Results section. ‡Study reported that a percentage of donors were taking antihypertensive medication but did not quantify the amount. NR, not reported.


<table>
<thead>
<tr>
<th>Source</th>
<th>Years after donation, mean (range)*</th>
<th>Diastolic blood pressure, mmHg N mean (sd) §</th>
<th>Use of anti-hypertensive medication(s), %</th>
<th>Controls</th>
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<tr>
<td>O’Donnell et al^37</td>
<td>6(3–18)</td>
<td>33 83 (10)</td>
<td>3</td>
<td>33 78 (12) …</td>
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<tr>
<td>Najarian et al^50</td>
<td>8(1–19)</td>
<td>63 80 (8)</td>
<td>32</td>
<td>58 80 (11) 44</td>
</tr>
<tr>
<td>Undurraga et al^53</td>
<td>11(1–21)</td>
<td>30 86 (13)</td>
<td>…</td>
<td>30 79 (9) …</td>
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<td>Talseth et al^54</td>
<td>11(10–12)</td>
<td>32 90 (10)</td>
<td>10</td>
<td>32 85 (10) …</td>
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<tr>
<td>Williams et al^57</td>
<td>13(10–18)</td>
<td>38 85 (25)</td>
<td>‡</td>
<td>16 82 (16) ‡</td>
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<td>Pooled estimate</td>
<td>196 84 (5)</td>
<td></td>
<td></td>
<td>161 80 (3)</td>
</tr>
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</table>

Fig. 2 Meta-analyses of long-term medical outcomes for hypertensive donors. Decrement in glomerular filtration rate (mL/min per 1.73 m²).

Graphed results are the difference between isolated medical abnormalities (IMA) and non-IMA donors on the change in outcome from before donation to after donation. (…) indicates missing value. Results were not pooled for I² > 50%.