Controversy on optimal blood pressure on haemodialysis: normotensive blood pressure values are essential for survival

Michael Schömig, Antje Eisenhardt and Eberhard Ritz

Department of Internal Medicine, Ruperto Carola University, Heidelberg, Germany

Introduction

Gérard London, our close friend and a distinguished investigator, argues that blood pressure (BP) values somewhat above the normal range are optimal for survival of patients on maintenance haemodialysis. We strongly disagree on this point and provide arguments that, despite the opinion of prominent investigators in this field, available evidence is in favour of the idea that BP values in the normotensive range are optimal for survival. We acknowledge, however, that definite controlled evidence is not yet available. In the absence of such evidence, clinicians must rely on a very powerful, although very rarely used instrument, i.e. clinical common sense.

Which BP values are considered optimal in the individual without renal disease?

It is of interest that the concept of what constitutes hypertensive BP values has been considerably revised downward in past decades. Originally, hypertension was considered to be BP >160/95 mmHg, but it was realized from the very beginning that the choice of any threshold is arbitrary, since BP readings in the general population exhibit a continuous distribution without a discernible threshold beyond which the risk increases abruptly. As shown in Table 1, today the International Society of Hypertension considers BP values of 120/80 mmHg as ‘optimal’ and values of no more than <130/85 mmHg as ‘normal’ [1]. This proposal is based on the consideration that in the general population according to epidemiological studies [2] the rate of cardiovascular events rises continuously with increasing systolic and diastolic BP values even in this range of BP values.

The issue here is whether the same low BP values are appropriate in dialysed patients as well.

Which BP values are found in haemodialysis patients?

According to the report of the US Renal Data System [3], diastolic BP values >90 mmHg are found only in a minority of dialysed patients, whereas systolic BP values above 140 mmHg, i.e. hypertension according to WHO/ISH [1], are noted in no less than 60% of dialysed patients. This is illustrated in Figure 1.

The majority of dialysis patients therefore exhibit isolated systolic hypertension. The main cause of this type of hypertension is diminished elasticity of central arteries with impaired ‘Windkessel’ function [4].

In contrast to what was thought in the past, however, it would be a mistake to consider isolated systolic hypertension as a harmless condition. A clear correlation exists between systolic blood pressure and cardiovascular mortality in elderly individuals with normal or low diastolic BP [5]. Reduction of BP by antihypertensive medication dramatically reduced cardiovascular (including cardiac) death in such patients [6–8]. Again, the issue remains whether the same is true for the dialysis patient with isolated systolic hypertension.

Which mechanisms are responsible for elevated BP in patients with renal failure?

There is no doubt that the genesis of BP elevation in renal failure is multifactorial [9]. According to the

Table 1. 1999 WHO/ISH hypertension guidelines (after Ref. [1])

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
</tr>
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<tbody>
<tr>
<td>Optimal BP</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Normal BP</td>
<td>&lt;130</td>
<td>&lt;85</td>
</tr>
<tr>
<td>High-normal BP</td>
<td>130–139</td>
<td>85–89</td>
</tr>
<tr>
<td>Grade 1 hypertension (mild)</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Grade 2 hypertension (moderate)</td>
<td>160–179</td>
<td>100–109</td>
</tr>
<tr>
<td>Grade 3 hypertension (severe)</td>
<td>≥180</td>
<td>≥110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥140</td>
<td>&lt;90</td>
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paradigm proposed by Guyton et al. [10], volume retention and hypervolaemia play a crucial. Figure 2 shows that sodium and water retention causes expansion of the plasma volume and the extracellular space, thus increasing venous return and cardiac output. If peripheral vascular resistance does not change, this constellation tends to elevate BP to some extent, but it is well known that acutely there may even be an adaptive decrease of peripheral vascular resistance [11]. The pronounced tendency of BP of volume-expanded individuals to rise in the long term is due, according to Guyton et al. to a secondary mechanism, so-called autoregulation, i.e. an increase of peripheral vascular resistance in a homeostatic effort to keep tissue perfusion constant. The simultaneous presence of elevated cardiac output and increased vascular resistance must obviously raise BP very effectively. Koomans et al. [12] documented that for any given degree of expansion of the extracellular space, peripheral vascular resistance and BP values are higher in patients with renal failure than in subjects with normal renal function (Figure 3). Factors contributing to elevated peripheral vascular resistance are (i) inappropriate activity of the renin–angiotensin system (RAS), comprising the systemic [13] as well as the local RAS in the vessel wall [14], (ii) increased sympathetic activity [15], and (iii) impaired endothelial cell-mediated vasodilatation [16] and others.

In apparent contradiction to the above construct, several authors reported that in dialysed patients, hypervolaemia did not cause an increase in BP. In the study of Luik et al. [11] volume expansion was associated with a decrease of the pressor peptides AVP and Ang II and presumably lower peripheral vascular resistance. The most plausible explanation for such discrepant results is that it takes considerable time before BP increases in response to hypervolaemia. As noted early on by Scribner et al. [17], when hypervolaemia has been present for several weeks, it will almost invariably cause an increase in BP, conversely lowering of BP by reversal of hypervolaemia takes several weeks [18–20]. Failure to consider the time factor may explain most of the apparent discrepancies in the literature.

**Fig. 1.** Predialytic BP values in patients on haemodialysis (after Mailloux et al. Am J Kidney Dis 1989; 323: 705–719).

**Fig. 2.** Pathophysiological aspects of the genesis of renal hypertension (after Ref. [10]).

**Early observations**

It is remarkable that no later than 8 weeks after the 1st dialysis patient, Clyde Shields, had been accepted for maintenance haemodialysis, Scribner et al. [17] reported that hypertension was one of the key problems of dialysis. As cited in a recent historical review [17] he had stated as early as 1960: 'As in the case of nephrectomised dogs, hypertension appears to be influenced by the size of the extracellular space. The combination of dietary sodium restriction and ultrafiltration during dialysis permits regulation of extracellular volume.'

Although the concept that hypervolaemia is a key factor in the genesis of hypertension has been with
us from the earliest days of chronic dialysis, such knowledge has been largely forgotten. This prompted Scribner to state recently [21]: ‘In the case of dialysis patients a low normal level of ECV is maintained by the powerful tool of ultrafiltration which, if properly used along with moderate dietary sodium restriction, is the only proven method of controlling BP in the haemodialysis population.’

What is the relationship between BP and survival in dialysed patients?

In a prospective study on haemodialysis patients it was shown recently that the BP amplitude was a significant predictor of cardiovascular death [22]. This is of note because a high BP amplitude reflects reduced aortic elasticity ('Windkessel'). This increases systolic stroke work of the heart by increasing peak systolic blood pressure on the one hand and lowers diastolic blood pressure by accelerated run off from central arteries into the periphery on the other hand. When Blacher et al. [22] considered a number of confounding factors by multivariate analysis, mean arterial blood pressure was no longer predictive, in contrast to the blood pressure amplitude.

The relationship between BP and survival in haemodialysis patients has remained quite controversial [23] and this is mainly due to the fact that, with rare exceptions [22], almost all of these studies have been retrospective (source of a number of biostatistical pitfalls) and short-term (precluding observation of long-term benefits from BP lowering). A retrospective long-term study of Charra et al. [24] argues strongly for a deleterious effect of even minor elevations of BP within the normal range.

In their retrospective analysis, these authors reported that survival in patients dialysed in Tassin was 20% better if mean pre-dialytic arterial pressure was below the median, i.e. 98 mmHg, than above (Table 2). These are values well within the range of the previous definition of normotension according to WHO, i.e. a mean arterial pressure (MAP) of 107 mmHg corresponding to a BP of 140/90 mmHg. It must be acknowledged, however, that the data of Charra et al. were not adjusted for confounders such as age, gender, and left ventricular hypertrophy. The discrepancy between the findings in two different cohorts of French patients [22,24] cannot be satisfactorily explained, but we favour the interpretation that the difference mainly reflects differences in the dialysis modalities that had been adopted, i.e. long, slow dialysis sessions with meticulous control of interdialytic weight gain in the former study and shorter dialysis sessions with higher interdialytic weight gain and consequently higher ultrafiltration rates in the latter study.

In apparent conflict with the conclusion of Charra et al. [24] other studies have since been reported in which the authors argue that low-normal BP values are associated with increased mortality and that moderately hypertensive BP values provide optimal survival [25–27]. The renal community was particularly shocked when Zager et al. [25] reported that a U-shaped relationship existed between post-dialytic BP and survival, mortality being increased both for low, but also for very high, BP values (Figure 4). For predialytic BP values other investigators [26,27] also found that survival was dramatically lower at predialytic BP values <120 mmHg (Figure 5). Such observational studies cannot tell, however, whether low blood pressure values are simply an indicator

Table 2. Survival rates at 10 years of HD as a function of mean arterial BP (MAP) (after Ref. [24]).

<table>
<thead>
<tr>
<th>MAP</th>
<th>Patient survival (%)</th>
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<tr>
<td>&lt;99 mmHg</td>
<td>85</td>
</tr>
<tr>
<td>&gt;99 mmHg</td>
<td>65</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
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Fig. 4. Mortality and systolic BP in haemodialysis patients (after Ref. [25]).

Fig. 5. Relative mortality risk (RR) and pre-dialysis systolic BP values in patients with end-stage renal disease (after Ref. [26]).
of high co-morbidity or a causative factor actively reducing life expectancy.

The potential effect of confounding factors and reverse causality

That mortality should be high at low BP values appears to be counter-intuitive. It would certainly be dangerous to conclude that it was necessary to raise blood pressure values in order to improve survival on dialysis.

One potential confounding factor could be that patients who are subjected to short dialysis sessions with low pre-dialytic systolic BP are at risk of intradialytic hypotension when high ultrafiltration rates must be achieved to cope with interdialytic weight gain. Indeed, in the high risk group of haemodialysis type 2 diabetic patients we found that the risk of cardiac death was increased by a factor of 3 when two or three hypotensive episodes occurred per week [28]. The idea that vascular catastrophes are provoked by hypovolaemia and hypotension is underlined by the observation of Haginoshita et al. [29]. In hypotensive patients they found a high rate of cardiovascular death, particularly from non-obstructive mesenteric infarction. Even if frankly hypotensive episodes do not occur, it is plausible that massive sympathetic activation is provoked by ultrafiltration in patients with pre-existing cardiac disease, and this is a deleterious factor contributing to cardiac arrhythmia and cardiac ischaemia [30].

Would this explanation be in line with what has been observed in non-renal patients? In a lucid analysis of the J-curve concept, i.e. the idea that aggressive lowering of diastolic BP below values of 85 mmHg increases the rate of cardiac events, Fletcher and Bulpitt [31] drew attention to the fact that low BP values per se characterized patients with poor cardiac function and high risk of cardiovascular death. Indeed, low BP was predictive of poor survival even in the placebo arm of studies on antihypertensive treatment, i.e. independent of intervention. Most remarkable in this context is the observation of the MRFIT study, where a correlation between low BP and cardiac death rate was noted, but this was found only during the first 2 years of observation. Beyond the third year, there was a monotonous linear positive relationship between BP and mortality. The authors interpreted this finding as indicating that low BP was a marker for high co-morbidity and high risk of premature death. This may well be a case of reverse causality: in these patients (and presumably also in renal patients) initially hypertension damages the heart and induces heart failure or ischaemic heart disease [32]. Paradoxically, although hypertension is the primary culprit, hypotensive BP values will then emerge ultimately as a predictor of adverse cardiac prognosis.

That this is a sensible explanation is further illustrated by the data of the Uruguayan Registry, recently reported by Mazzuchi et al. [33] who found that low predialytic BP values were predictive of death during short observation periods, while mortality in long-term observations was less in patients with normal compared to higher BP values.

In order to find some common ground with Dr London, we agree that low BP and low BP is not necessarily always the same. In order to evaluate the impact of BP on prognosis, it is important to consider the context, i.e. which mechanisms are responsible for low BP and which modalities of treatment are applied. It follows that inflexible BP management according to unchangeable guidelines, not taking into account the individual patient and the above factors, will definitely guarantee poor outcomes.

The time factor

It has proved very difficult to show that lowering of BP provides survival benefit in middle-age individuals with mild to moderate hypertension. Indeed in the Framingham study [34], it took no less than 10 years before a survival benefit of antihypertensive treatment could be demonstrated. Obviously in populations with low cardiovascular event rates, considerable time is required before the cumulative benefit becomes noticeable. This should be contrasted with studies in elderly patients [6–8], in whom a survival benefit was demonstrable within a relatively short period. Although the cardiovascular event rate is very high in dialysis patients, many of the observational studies [25–27] may simply have not been of sufficient duration to observe the slowly accumulating survival benefit which had been noted in the Tassin study [24]. It also follows from this consideration that there may not be a uniform ‘optimal blood pressure’ which is valid for all patients. In dialysis patients with poor life expectancy one can presumably be considerably more lax with the target BP.

What is optimal BP in the individual dialysis patient and how can this be achieved?

It is interesting that most centres who reported favourable survival at low normal pre-dialytic BP values treated their patients using long dialysis sessions and low ultrafiltration rates. In addition they reduced dietary sodium intake and some of them also adopted lowish dialysate sodium concentrations [20,35,36]. Although long-term mortality data are not available, it is of particular interest in this context that early observations [37] and more recent controlled studies reported lower BP values and even regression of left ventricular hypertrophy when patients were subjected to daily dialysis. This was true even when dialysis efficiency, as measured by Kt/V, was kept constant [38].

The recommendation to achieve normotension by inducing a negative sodium balance and by achieving
‘dry weight’ may seem simple, but it is extremely difficult to implement in clinical practice. Unfortunately we have not progressed much beyond the empirical approach of Thomson et al. [39] who aimed at achieving ‘dry weight’ by removing fluid by ultrafiltration until patients developed symptoms (which in itself is of course undesirable). Further complexity is introduced by the fact that body weight is the composite result of hydration states and lean body mass, as recently emphasized by Chazot et al. [18], so that ‘dry weight’ must be reassessed periodically, particularly in the early months of dialysis treatment.

**What is a sensible practical approach?**

We believe (i) that dialysis patients do not dramatically differ from the general population, where treatment of isolated systolic hypertension was beneficial, and (ii) that systolic BP values well below 140 mmHg are optimal for long-term survival. This statement is true only for patients who do not have major cardiac disease and tolerate dialysis sessions without hypertensive episodes. The survival benefit takes time to materialize and patients with poor prospects of survival may not live long enough to experience the benefits of strict BP control.

The diastolic BP is strongly influenced by vascular remodelling. Paradoxically, low diastolic BP values, far from being beneficial, may thus point to a high cardiovascular risk as they do in the general population [40], but this is much less clear in dialysis patients because of the many confounding factors. We have very few options to interfere with vascular remodelling in contrast to high systolic BP, which we can influence by therapeautic measures.

Although not directly related to the BP issue, we also feel it is an important matter for future investigations to provide proof whether or not beta blockers protect against ultrafiltration-induced sympathetic activation, independent of their BP-lowering effect, as suggested recently [30].

In a nutshell, we believe that for the dialysis patient the ‘optimal BP’ is the lowest pressure which is well tolerated, i.e. which is consistent with acceptable well being and no episodes of intradialytic hypotension.

**References**

35. Özkahya M, Ok E, Cirit M et al. Regression of left ventricular hypertrophy in haemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs. *Nephrol Dial Transplant* 1998; 13: 1498–1493