Chronic Limb Remote Ischemic Conditioning may have an Antihypertensive Effect in Patients with Hypertension

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ABSTRACT: Hypertension is the leading preventable risk factor for all-cause morbidity and mortality worldwide. Despite antihypertensive medications have been available for decades, a big challenge we are facing is to increase the blood pressure (BP) control rate among the population. Therefore, it is necessary to search for new antihypertensive means to reduce the burden of disease caused by hypertension. Limb remote ischemic conditioning (LRIC) can trigger endogenous protective effects through transient and repeated ischemia on the limb to protect specific organs and tissues including the brain, heart, and kidney. The mechanisms of LRIC involve the regulation of the autonomic nervous system, releasing humoral factors, improvement of vascular endothelial function, and modulation of immune/inflammatory responses. These underlying mechanisms of LRIC may restrain the pathogenesis of hypertension through multiple pathways theoretically, leading to a potential decline in BP. Several existing studies have explored the impact of LRIC on BP, however, controversial findings were reported. To explore the potential antihypertensive effect of LRIC and the underlying mechanisms, we systematically reviewed the relevant articles to provide an insight into the novel therapy of hypertension.

Key words: remote ischemic conditioning; hypertension; antihypertensive effect; blood pressure

1. Introduction

Hypertension is the leading cause of attributable deaths and burden of disease globally, which is also one of the important preventable risk factors for cardiovascular disease (CVD)[1]. The pathogenesis responsible for hypertension include overactivation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), increased chronic inflammatory responses, and dysregulation of the immune system [2]. Despite great efforts have been made and extensive studies have been conducted over the past decades, the control of hypertension is still not satisfying [3, 4]. This situation requires us to search for novel pharmaceutical or non-pharmaceutical means to optimize the therapeutic approach for hypertension. Limb remote ischemic conditioning (LRIC) may be a new method worthy to be further explored.

LRIC includes repetitive inflation-deflation of a pneumatic cuff on the limb, which can trigger endogenous
protective effect to remote organs such as the heart, brain, and kidney by neural, humoral, and immune/inflammatory pathways [5, 6]. Numerous studies have demonstrated that LRIC is a promising treatment in various clinical conditions, especially in ischemia-reperfusion injuries [5, 7-10]. Studies have explored the impact of LRIC on blood pressure (BP) with controversial results in recent years. The BP-lowering effect of LRIC was observed in several studies [11-17], but the results were not consistent in others [18-24]. Due to the heterogeneity in participant selection and LRIC protocols, it is necessary to make a systematic analysis of these studies to explore whether LRIC has the potential to be a novel therapeutic method for hypertension.

We systematically analyzed the clinical research data about the impact of LRIC on BP which was published on PubMed, EMBASE, Cochrane Library databases, and Web of Science up to Jan 2021, to explore whether LRIC has a BP-lowering effect and its potential mechanisms. In addition, we will provide an overview of the ongoing clinical trials and discuss the challenges we are going to face in the future.

Table 1. The effect of LRIC on BP in healthy volunteers.

| Study         | N. Participants | Design | Comparator | LRIC protocol                  | Frequency, Duration | Antihypertensive effect |
|---------------|-----------------|--------|------------|--------------------------------|---------------------|-------------------------|
| Kimura [24]   | 20 healthy      | RCT    | Control    | 1×5 min ischemia                | 6×daily, 1 month    | NO                      |
| Jones [18]    | 18 healthy      | RCT    | Control    | 4×5 min ischemia/5min reperfusion | 3×weekly, 8 weeks   | NO                      |
| Banks [20]    | 10 healthy      | Cohort | None       | 4×5 min ischemia/5min reperfusion | 1×daily, 9 days     | NO                      |
| Zagidulin [25]| 20 healthy      | RCT    | Sham control| 3×5 min ischemia/5min reperfusion | Once-only           | NO                      |
| Khalilulin [21]| 40 healthy     | RCT    | Sham control| 3×5 min ischemia/5min reperfusion | Once-only           | NO                      |
| Muller [22]   | 40 healthy      | RCT    | Sham control| 3×5 min ischemia/5min reperfusion | Once-only           | NO                      |
| Li [26]       | 24 healthy      | Cohort | None       | 5×5 min ischemia/5min reperfusion | Once-only           | YES                     |
| Graua [27]    | 20 healthy      | Cohort | None       | 4×5 min ischemia/5min reperfusion | Once-only           | YES                     |

The cuff pressure is about 200-220mmHg or at 20/50mmHg above systolic BP to induce ischemia.

2.1.1 The effect of once-only LRIC on BP

Muller et al. carried out a randomized controlled trial (RCT) of 40 young healthy volunteers and found that once-only LRIC treatment consisting of three cycles of 5min ischemia followed by 5min reperfusion did not affect BP [22]. With the same LRIC plan, the same conclusion was drawn from the RCT conducted in healthy subjects by Khalilulin et al. and Zagidullin et al. [21, 25]. However, other prospective cohorts showed that once-only LRIC therapy could temporarily lead to a drop in BP for healthy people [26, 27]. The above-mentioned results seem insufficient for us to draw a certain conclusion.

2. Whether LRIC has an antihypertensive effect in humans?

22 clinical studies involving 665 participants showed the effect of LRIC on BP according to a comprehensive literature retrieval (see Table 1-2), however, these studies were with heterogeneities. First, different ranges of subjects were included. Both healthy volunteers and CVD patients were enrolled in 2 studies [25, 26], healthy volunteers with normal BP were included in 6 studies [18, 20-22, 24, 27], patients with hypertension or CVD were enrolled in 14 studies [11-16, 19, 23, 28-33]. Second, different LRIC schemes were used. LRIC therapy for once or twice only was performed in 10 studies [21-23, 25-27, 30-33], a long-term repeated LRIC therapy was applied in 12 studies [11-16, 18-20, 24, 28, 29]. Thus, we classified these relevant articles according to different participant selection and LRIC schemes to clarify whether LRIC has an antihypertensive effect in specific populations, the details of these studies are listed in Table 1 and 2.

Therefore, we will further discuss the effect of long-term repeated LRIC on BP in this review (See Table 1).

2.1.2 The effect of repeated LRIC on BP

Kimura et al. found that a LRIC scheme which was performed a single 5-min ischemia six times a day consecutively for one month didn’t reduce BP, but endothelium-dependent vasodilation was shown to improve in healthy subjects [24]. The study of Banks et al. showed that nine consecutive days of once-daily LRIC treatment including four cycles of 5min ischemia/5min reperfusion cannot lead to a drop in BP [20]. Jones et al. also demonstrated that LRIC treatment which was three times a week for eight weeks improved endothelial function without lowering BP [18]. However, another
study by Jones et al. showed a significant decline in BP after a 7-day intervention of once-daily LRIC therapy [12]. In this study, participants were recruited with an average baseline BP of 138±6/73±6 mmHg which should be defined as prehypertension rather than healthy volunteers. In summary, LRIC seems to have no significant effect on BP in normotensive or healthy volunteers (floor effect)(See Table 1).

Table 2. The effect of LRIC on BP in patients with CVD or hypertension.

| Study            | No. Participants | Design   | Comparator | LRIC protocol | Frequency, Duration | Antihypertensive effect |
|------------------|------------------|----------|------------|---------------|---------------------|-------------------------|
| Kuusik [33]      | 111, PAD         | RCT      | Sham control | 4×5min ischemia/5min reperfusion | Once-only | NO          |
| He [23]          | 49, AIS          | RCT      | Sham control | 4×5min ischemia/5min reperfusion | Twice-only | NO          |
| Kepler [32]      | 98, vascular surgery | RCT | Sham control | 4×5min ischemia/5min reperfusion | Once-only | NO          |
| Zhao [31]        | 20, AIS          | Cohort   | None       | 3×5min ischemia/5min reperfusion | Once-only | NO          |
| England [30]     | 26, AIS          | RCT      | Sham control | 4×5min ischemia/5min reperfusion | Once-only | NO          |
| Li [26]          | 10, MCA stenosis | Cohort   | None       | 5×5min ischemia/5min reperfusion | Once-only | NO          |
| Meng [28]        | 58, SIAS         | RCT      | Sham control | 5×5min ischemia/5min reperfusion | 2×daily, 30 days | NO          |
| Zagidulin [25]   | 30, angina pectoris | RCT | Sham control | 3×5min ischemia/5min reperfusion | Once-only | YES         |
| Medias [11]      | 1, normo-/pre-HTN | Case study | Self | 3×5min ischemia/5min reperfusion | 2×daily, 3 days | YES         |
| Jones [12]       | 13, pre-HNT     | Cohort   | None       | 4×5min ischemia/5min reperfusion | 1×daily, 7 days | YES         |
| Medias [13]      | 1, normo-/pre-HTN | Case study | Self | 3×5min ischemia | 2×daily, 7 days | YES         |
| Medias [14]      | 1, normo-/pre-HTN | Case study | Self | 3×5min ischemia | 2×daily, 10 days | YES         |
| Medias [19]      | 1, normo-/pre-HTN | Case study | Self | 3×5min ischemia | 1×daily, 10 days | NO          |
| Pujara [29]      | 20, CF LVADs     | RCT      | Control    | 3×5min ischemia/5min reperfusion | 2×daily, 30 days | YES         |
| Pryds [15]       | 22, CIHF         | Cohort   | None       | 4×5min ischemia/5min reperfusion | 1×daily, 1 month | YES         |
| Tong [16]        | 15, HTN          | Cohort   | None       | 3×5min ischemia/5min reperfusion | 1×daily, 1 month | YES         |

The cuff pressure is about 200-220mmHg or at 20/50mmHg above systolic BP to induce ischemia. PAD, peripheral arterial disease; AIS, acute ischemic stroke; MCA, middle cerebral artery; SIAS, symptomatic intracranial arterial stenosis; HTN, hypertension, CF LVADs, continuous flow left ventricular assist devices; CIHF, chronic ischemic heart failure.

2.2 The effect of LRIC on BP in patients with CVD or hypertension

2.2.1 The effect of once-only LRIC on BP

By evaluating the safety and feasibility of LRIC in patients with unilateral middle cerebral artery (MCA) stenosis, Li et al. reported that once-only LRIC protocol did not affect BP and heart rate in these patients [26]. The study of England et al. showed that once-only LRIC therapy had neither short-term nor delayed effect on central arterial pressure in patients with acute ischemic stroke (AIS) [30]. Other studies also draw similar conclusions that once or twice LRIC treatment only was not enough to reduce BP in patients with CVD [23, 31-33]. Meng et al. compared changes in BP before and after each LRIC treatment in patients with symptomatic intracranial artery stenosis (SIAS) and found that LRIC had no short-term hypotensive effect. However, BP levels before and after one month of therapy were not measured in this study, thus, the effect of long-term repeated LRIC on BP cannot be noticed from the result of this research.

Chronic LRIC has a potential antihypertensive effect.
[28]. Zagidullin’s study of 30 angina pectoris patients was the only one reporting that once-only LRIC training could lead to a drop in peripheral systolic BP [25]. Therefore, we conclude that once-only LRIC therapy seems not enough to reduce BP in individuals with CVD or hypertension (See Table 2).

2.2.2 The effect of long-term repeated LRIC on BP

Medias is the first scholar who explored whether LRIC can reduce BP. He carried out a series of self-control studies by implementing LRIC on himself, a normotensive or prehypertensive person, and found that twice-daily LRIC treatment had both a short-term and delayed BP-lowering effect [11, 13, 14]. However, this effect disappeared in the circumstance of once-daily LRIC therapy [19]. Pujara et al. found that twice-daily LRIC performed over a period of one month could result in a significant reduction in average arterial pressure (MAP) in patients with continuous flow left ventricular assist devices (CF LVADs) [29]. Pyrds et al. reported that LRIC performed once a day for one month could reduce systolic BP in patients with chronic ischemic heart failure (CHIF) [15]. However, office BP measurement is not ideal compared with ambulatory BP measurement (ABPM). The study by Tong et al. demonstrated the impact of chronic LRIC on BP by using both office BP measurement and ABPM for the first time, which showed that one month of once-daily LRIC treatment could lead to a significant fall in systolic BP and diastolic BP in patients with hypertension [16]. In a word, long-term repeated LRIC therapy seems to have a potential antihypertensive effect in those with hypertension or CVD (See Table 2).

2.3 Speculation of long-term repeated LRIC may have an antihypertensive effect on hypertension

Considering all the available evidence mentioned above, the following speculations can be made. In summary of 8 clinical studies including 192 subjects, the first speculation is that neither LRIC performed once nor repeated for a long time has a significant BP-lowering effect on healthy volunteers with normal BP [18, 20-22, 24-27]. Secondly, after analyzing 8 studies involving 402 patients with CVD or hypertension, we confer that LRIC treatment performed only once seems insufficient to trigger the BP-lowering effect [23, 25, 26, 28, 30-33]. In addition, we presume that long-term repeated LRIC therapy may provide an alternative applicable intervention to treat hypertension, evidence of which was from 71 subjects involved in 8 studies [11-17, 19, 29].

Our team conducted an animal experiment and designed a clinical trial to further verify these speculations. Our completed animal experiment demonstrated that LRIC therapy once daily for six consecutive weeks could reduce MAP and attenuate vascular remodeling by regulating immune or inflammatory responses in spontaneously hypertensive rats (SHR), but these changes did not occur in normotensive Wistar-Kyoto rats (WKY) [34]. A clinical trial was designed by us to demonstrate the antihypertensive effect of chronic LRIC is recruiting participants with prehypertension and mild hypertension currently (NCT03566654).

In a word, long-term repeated LRIC seems to be a promising novel antihypertensive therapy for hypertension. However, the mechanisms of the BP-lowering effect by chronic LRIC therapy still need to be clarified. Next, we will explore the intersections between the pathogenesis of hypertension and the endogenous protective mechanisms of LRIC to clarify this.

3. Potential mechanisms of the antihypertensive effect of LRIC

BP homeostasis is determined by the complex interplay of cardiac output, peripheral vascular resistance, and blood volume. Any abnormality in the process of BP regulation can directly or indirectly lead to sustained elevated BP. Activated SNS and RAAS, chronic immune or inflammation response, and aberrant vascular endothelial function are well-established pathogenesis of hypertension [2]. Existing studies have presented many intersections between the endogenous protective mechanisms of LRIC and the pathogenesis of hypertension [5-7]. Therefore, it is reasonable to hypothesize that LRIC can repress the pathogenesis of hypertension through multiple pathways, thereby exerting a BP-lowering effect (Fig. 1).

3.1 Regulation of autonomic nervous system

Patients with hypertension are usually accompanied by continuous imbalance of the autonomic nervous system (ANS), this imbalance is characterized by increased SNS activity and decreased parasympathetic nerve system (PNS) activity [35]. Current treatments aiming to inhibit SNS activity, such as central SNS suppressing drugs, peripheral alpha- and beta-adrenergic receptor blockers, and renal sympathetic denervation, can significantly reduce BP[36]. Aside from SNS inhibition, stimulation of the PNS pathway can reduce BP as well [37, 38]. Therefore, restoring the balance of ANS is one of the important targets for antihypertensive therapy. LRIC treatment has been demonstrated by preclinical and clinical studies to have a positive effect on ANS.
3.1.1 Evidence from animal experiments

In animal experiments, Ogawa et al. found that sympathetic nerves partly mediated the protective effect of ischemic conditioning against injuries in rats caused by renal ischemia-reperfusion, which could be offset by renal denervation [39]. Tsutsui et al. demonstrated that ischemic conditioning played protective roles in the rat model of ischemia/reperfusion-induced acute kidney injury for both the ischemia period and the reperfusion period. It suppressed the enhanced renal SNS activity during ischemia and decreased norepinephrine release during reperfusion time [40]. Apart from the sympathoinhibitory effect, LRIC played an important role in enhancing PNS activity as well. Through constructing multiple myocardial ischemia-reperfusion injury models, some others found that vagotomy, inhibition of the dorsal motor nucleus of the vagus (DMV), or atropine administration could eliminate the protective effects of LRIC [41-45]. Furthermore, stimulation of the vagus or DMV neurons could mimic the protective effect of LRIC [46-48].

3.1.2 Evidence from clinical studies

In clinical studies, Lambert et al. reported that LRIC could attenuate and delay SNS activation induced by ischemia-reperfusion. In his study of 30 healthy volunteers, the randomized intervention of LRIC or no-LRIC was applied right before experimental ischemia-reperfusion. Participants in the control group had a 70% increase of SNS activity in the early phase of ischemia and a 101% increase in the late phase; those in the LRIC group only had a 40% increase in SNS activity which was delayed to the late phase of ischemia [49]. The study by Enko et al. showed that LRIC could enhance the activity of PNS and induce vasodilation in healthy volunteers [50]. In summary, we suppose that LRIC can lead to a drop in BP by decreasing SNS activity and increasing PNS activity.

3.2 Improve vascular endothelial function and vascular remodeling

The endothelium is a key regulator of vascular tone, which can release a host of vasoactive substances including vasodilating factors and vasoconstricting factors to regulate vascular resistance and influence BP [2, 51, 52]. Patients with hypertension are usually accompanied by endothelial dysfunction which is characterized by decreasing the production or bioavailability of endothelium-derived relaxing factors, especially nitric oxide (NO), and increasing the release or responsiveness of vasoconstrictor factors [2, 51, 52]. Some studies supposed that endothelial dysfunction preceded the establishment of essential hypertension, but others suggested that endothelial dysfunction was a consequence of elevated BP. It seems to be a vicious cycle as deterioration of one may worsen the other, promoting
pathological vascular remodeling and leading to poor prognosis [51-53]. Hence the early recognition and timely management of endothelial dysfunction and vascular remodeling are beneficial to reduce BP and prevent hypertension associated end-organ damage [54].

3.2.1 Evidence from animal experiments

Animal experiments have suggested that endothelium-derived factors play an important role in the protective effect of RIC. Rassaf et al. found that LRIC therapy increased the level of circulating nitrite (a key reservoir for NO) in mice, which was associated with the cardioprotection of LRIC[55]. He et al. reported that up-regulation of PI3K/Akt/eNOS/NO pathway mediated the protective role of RIC in a rat model of liver transplantation [56]. Aggarwal et al. reviewed the role of endothelin in RIC-induced cardioprotection, especially underlying endothelium-derived factors. He concluded that NO was a central mediator in the protective effect of RIC[57]. Other vasoactive substances, such as adenosine, prostacyclin, calcitonin gene-related peptides, angiotensin II (Ang II), and thromboxane A2, may play roles as well [57-61]. Besides, Gao et al. demonstrated that chronic LRIC benefited both the conducting and the resistance arteries of SHR. It ameliorated hypertrophic vascular remodeling by suppressing the deposition of the extracellular matrix in conducting arteries and decreasing the collagen production and the degree of smooth muscle cell hypertrophy in the resistance arteries [34].

3.2.2 Evidence from clinical studies

The fact that the improvement of endothelial function and vascular remodeling by RIC procedure has been observed in numerous clinical studies. Kimura et al. [24] and Jones et al. [12, 18] found that repeated LRIC treatment augmented endothelium-dependent vasodilation in healthy adults. Moro et al. reported that once-only LRIC therapy was sufficient to improve endothelium-dependent vasodilation in healthy or hypertensive elderly subjects [62]. In stroke patients, the evidence that endothelium-dependent vasodilation improved after two weeks of LRIC treatment has been demonstrated by Hyngstrom et al. [63]. Similarly, Liang et al. reported that chronic LRIC improved endothelium-dependent vasodilation in coronary heart disease (CHD) patients [64]. Apart from improving vasodilation, LRIC may alleviate continuous contraction of the blood vessel by inhibiting the synthesis of endothelin-1 (ET-1) [65-67]. Gao et al. demonstrated that chronic LRIC could improve the situation of vascular stiffness in patients with prehypertension and mild hypertension, which was consistent with the results in her animal experiment [34]. In conclusion, we hypothesize that LRIC may exert its antihypertensive effect by improving endothelial function and vascular remodeling.

3.3 Regulation of immune/inflammatory responses

Numerous preclinical and clinical studies highlight the relationship between hypertension and prolonged activation of immune or inflammatory responses [2]. Chronic activation of innate and adaptive immune systems promotes the accumulation of immune cells and autoantibodies in the heart, brain, kidney, and blood vessel, which leads to hypertension by weakening BP regulation of these organs [2, 68, 69]. Researches have shown that immune-targeting therapies not only reduced BP in experimental hypertensive animals [70, 71] but also improved BP control in hypertensive patients with autoimmune diseases [72, 73]. Although the risk-benefit ratio of immuno-targeting therapies seems to be high, it is still being considered as one of the important approaches in treating hypertension and CVD in the future [69, 74]. In contrast, LRIC could exert its protective effect by regulating immune/inflammatory response with few side effects [75], which might be a therapy to hypertension of good potential.

3.3.1 Evidence from animal experiments

In a lipopolysaccharide-induced mouse model, Kim et al. found that LRIC could attenuate inflammatory response and improve the survival rate of mice. The mechanisms of this intervention were that LRIC decreased circulating pro-inflammatory (such as TNF-α, IL-1β, and IL-6), increased plasma anti-inflammatory factors (such as IL-10), and reduced infiltration of neutrophil in the liver [76]. Zhou et al. reported that LRIC improved lung function of a cardiopulmonary bypass (CPB) induced pulmonary injury model in rats through increasing IL-10 and IL-4 anti-inflammatory cytokines and reducing neutrophil infiltration in alveoli [77]. Wei et al. proved that chronic LRIC could reduce the infarct size and improve survival outcome in a myocardial infarction model of rats. Which was mediated by lowering the production of circulating TNF-α, IL-1β, and MCP-1 and lessening the macrophage/neutrophil infiltration in the infarct border zone [78]. Chen et al. [79] and Heusch et al. [80] regarded that LRIC could shift splenic immune response toward a favorable systemic immune milieu, thereby, protecting the brain and heart from ischemic injury. Gao et al. demonstrated that LRIC had a direct immunomodulation effect on SHR. In her study, once-daily LRIC for six consecutive weeks not only decreased the inflammatory profiles including circulating monocyte, natural killer T cells, and pro-inflammatory factors (TNF-α, IL-1β, and
CXCL1) but also increased the anti-inflammatory factors (IL-10 and IL-13) [34].

3.3.2 Evidence from clinical studies

Contrary to animal experiments, most clinical trials were unable to confirm the effect of RIC on inflammatory response. Konstantinov et al. found that LRIC could suppress the transcription of proinflammatory genes in human leukocytes [81]. Shimizu et al. demonstrated these changes in proinflammatory gene expression could lead to functional changes in neutrophils, including reduced adhesion, phagocytosis, and exocytosis [82]. He et al. carried out an RCT in 90 elderly patients following colon surgery and found that LRIC could improve postoperative cognitive function by inhibiting inflammatory response [83]. RCT conducted by Wang et al. showed that LRIC may be a protective therapy in coronary artery bypass graft surgery, which can be partially attributed to the reduced production of inflammatory factors(IL-6, IL-8, TNF-α) [84]. In summary, we speculate that LRIC may reduce BP by modulating immune/inflammatory response.

3.4 Other mechanisms

Overactivated RAAS plays an important part in the pathogenesis of hypertension. Most current drugs for hypertension, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid antagonists, aim to block the influence of RAAS on BP [36]. However, only a few studies reported the impact of LRIC on RAAS. One clinical study showed that LRIC might exert its neuroprotective effects by reducing the level of circulating Ang II in stroke patients [65]. However, an animal experiment showed that LRIC might resist myocardial ischemia-reperfusion injury through the preconditioning of Ang II [85]. Therefore, it remains to be further explored whether LRIC reduces BP by inhibiting RAAS.

The increased releasing of stromal derived factor 1α (SDF-1α) may be another potential mechanism. The study from Tong et al. has demonstrated that plasma SDF-1α increased after chronic LRIC therapy. This increase of SDF-1α was associated with a fall in BP and an improvement in endothelial function [16]. Evidence from another study also demonstrated that LRIC might exert its protective effects by increasing SDF-1α [86].

4. Future Perspectives of LRIC in the treatment of hypertension

It seems that chronic LRIC has a potential antihypertensive effect on hypertension from the available data so far. However, further studies are required to clarify this phenomenon and the exact mechanisms involved. The ongoing HOPE study (NCT03566654) aims to explore the BP-lowering effect of chronic LRIC on patients with prehypertension or early-stage hypertension. The SERIC-EH study (NCT03945305) intends to evaluate the safety and efficacy of chronic LRIC on hypertensive patients who are taking antihypertensive drugs and still lack normal BP control. Other ongoing studies are accessing the BP-lowering effect of LRIC on women with pre-eclampsia (NCT03323762), patients with chronic kidney disease and hypertension (NCT03236350), and healthy volunteers or essential hypertensive patients (NCT02414997). These studies will provide compelling evidence for the safety and efficacy of LRIC on the treatment of hypertension in a different population, thereby providing a novel and effective alternative treatment.

However, we are still facing several problems about implementing chronic LRIC on more hypertensive patients. Firstly, the antihypertensive effects of chronic LRIC should be further validated in large-scale and rigorous RCTs in patients with elevated BP. Secondly, despite the beneficial effects of LRIC on multiple organs have been demonstrated, the optimal scheme of LRIC for efficiently reducing BP remains to be explored. Thirdly, the mechanisms of LRIC are mostly investigated in the ischemia-reperfusion injury model of different organs, which seems cannot be directly applied in the case of hypertension. What’s more, the impact of co-morbidities and co-medications on RIC therapy in hypertension patients must be considered in future clinical trials based on previous experience and evidence [87, 88]. Most importantly, accurate BP measurement (using ABPM as a gold standard) should be adopted with serious-minded across different studies. Therefore, future efforts should be focused on addressing these questions mentioned above.

5. Conclusion

In conclusion, chronic LRIC may restrain the pathogenesis of hypertension and lower BP through multiple pathways including regulation of ANS, improvement of vascular endothelial function, and modulation of immune/inflammatory responses. However, before widely applying chronic LRIC as a treatment of hypertension, further studies are warranted to build a solid foundation so as to validate the beneficial effect of LRIC and its adverse effects.

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Conflicts of Interest

The authors declare no conflict of interest.

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