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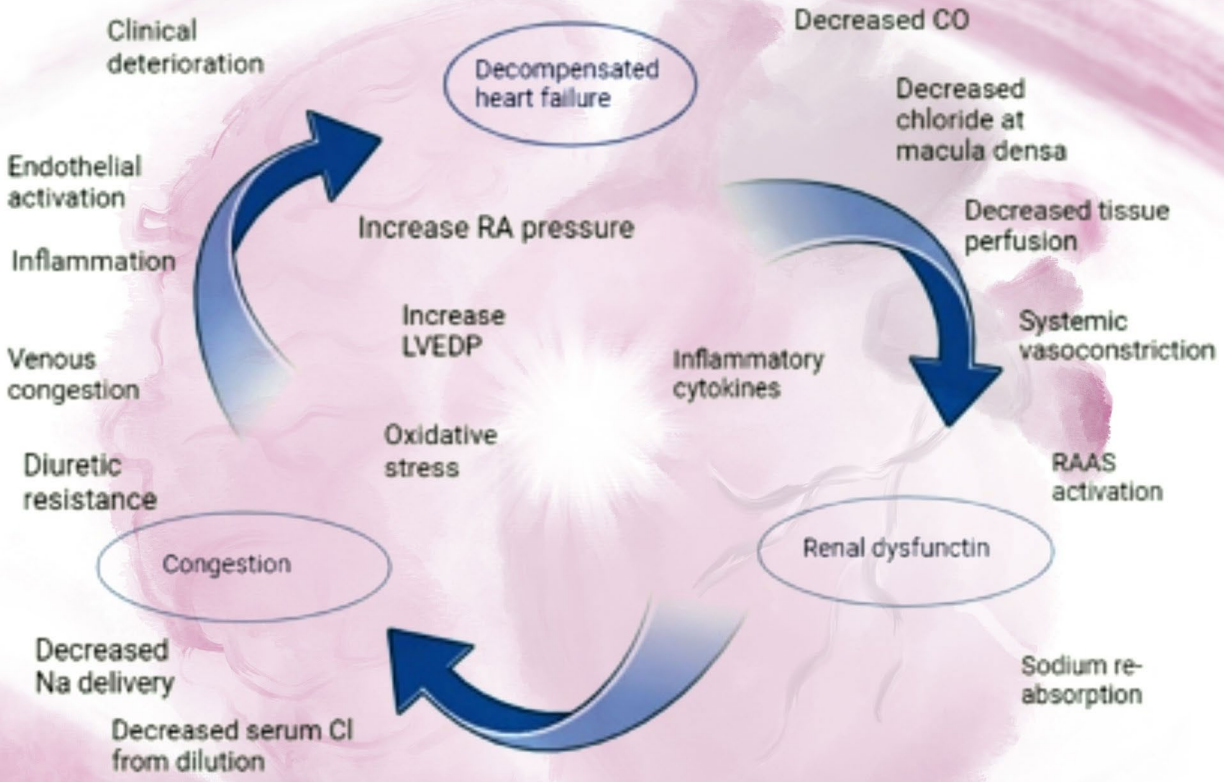

Hypochloremia in heart failure: A new prognostic and therapeutic aspect of refractory heart failure

ACCSCIENCE PUBLISHING
Volume 2 · Issue 1
February 2024
ISSN: 2972-4139 (Online)

Online ISSN: 2972-4139

Brain & Heart

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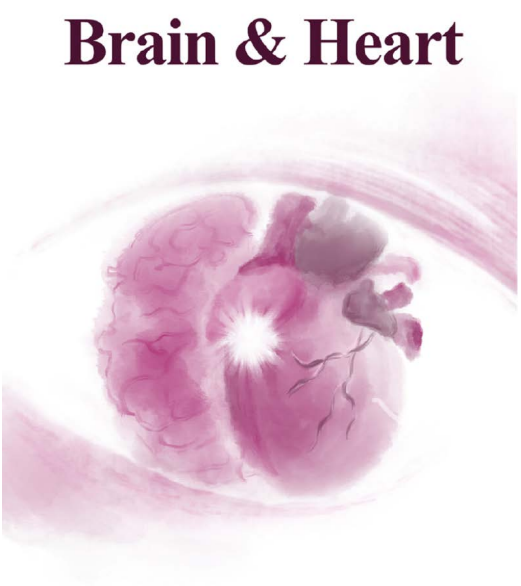

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Volume 2 • Issue 1 • February 2024
ISSN 2972-4139 (online)

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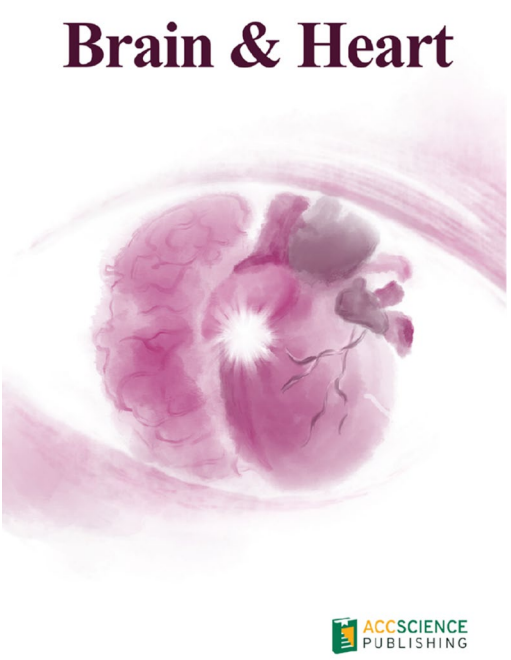

BRAIN & HEART

ISSN: 2972-4139 (online)

Editorial and Production Credits

Publisher: AccScience Publishing
Managing Editor: Naomi Li
Production Editor: Sharmila Velapasamy
Article Layout and Typeset: Sinjore Technologies (India)

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REVIEW ARTICLE

Hypochloremia in heart failure: A new prognostic and therapeutic aspect of refractory heart failure

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Abstract

Heart failure (HF) is one of the most common cardiovascular diseases, bearing a significant burden of morbidity, mortality, and disability. Low serum chloride (Cl) levels have been observed to play an important role in predicting mortality and planning management strategies for HF. This review aims to investigate the influence of hypochloremia on individuals suffering from HF and its correlation with various underlying pathophysiological mechanisms. We conducted a literature review of articles published in the past 10 years, employing specific keywords to identify relevant studies from databases such as PubMed, Google Scholar, EBSCO, and Biomed Central. There is a significant paucity of studies relevant to low serum Cl levels in patients with HF. We found that hypochloremia is commonly observed in HF cases, an often overlooked aspect in clinical setting, and is associated with poor outcomes. Substantial evidence supports the notion that hypochloremia can worsen HF, reduce the response to guideline-mediated therapies, and increase mortality. Hypochloremia activates numerous neurohormonal mechanisms, further worsening the cardiorenal circuit in HF. Furthermore, low Cl levels are associated with the development of diuretic resistance, making HF difficult to manage, particularly with loop diuretics. Studies reveal associations between hypochloremia and various kinases, with a particular emphasis on with-no-lysine kinases. These kinases, involved in regulating salt and water reabsorption, exacerbate the condition when Cl levels are low. Notably, a low serum Cl level is associated with high mortality in HF and worsens the condition. HF with hypochloremia poses challenges in treatment and should, therefore, be considered in management.

Keywords: Heart failure; Serum chloride; Hypochloremia; Electrolytes; Mortality

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Citation: Raza S, Ditto SA. Hypochloremia in heart failure: A new prognostic and therapeutic aspect of refractory heart failure. *Brain & Heart*. 2024;2(1):2257. https://doi.org/10.36922/bh.2257

Received: November 15, 2023

Accepted: January 12, 2024

Published Online: February 15, 2024

1. Introduction

Heart failure (HF) is the most common cardiovascular disease (CVD), affecting nearly 6.2 million adults in the United States. The incidence approaches 21/1000 in individuals above 65 years of age.[1] HF is an increasing epidemic, with an approximate prevalence of 37.7 million people worldwide. Based on the statistics from the USA, the total cost for individuals with HF has been projected to increase from US$20.9 billion in 2012 to

US$53.1 billion by 2030.[2] One study reported that, in 2006, Pakistan had 2.8 million subjects with HF.[3]

HF is a severe and resource-intensive condition that leads to early mortality, high morbidity, impaired functional status, low quality of life, and polypharmacy. HF is characterized by symptoms such as shortness of breath, orthopnea, pedal edema, and signs such as elevated jugular venous pressure and pulmonary edema.[4] Most guidelines refer to HF as chronic established HF, which can be graded according to the functional classification of the New York Heart Association.[4] To date, patients with HF are usually categorized into those with reduced ejection fraction (EF) (HF with reduced EF [HFrEF]; EF < 40%), moderately reduced (EF < 40 – 49%), and preserved (EF > 50%).[5] Many population-based cohorts have described the factors that commonly predispose individuals to HF, of which coronary artery disease, hypertension, diabetes mellitus, obesity, and smoking are notable.[5] HF with preserved EF (HFpEF) represents approximately 50% of all HF in most cases.[6] The studies that reported long-term follow-up data and standardized criteria show that mortality in HF is high. More recent studies have reported nearly 50% at 5 years.[6] The 1-year mortality rate after an HF incident in the UK population was reported to be as high as 32%, of which 43% was attributed to CVDs.[7]

There are many well-known independent predictors of prognosis in HF.[8] The outcome of HF remains poor in terms of mortality, frequent hospitalizations, and worsening of HF, comparable to that of many malignancies. Advanced age, previous hospitalization, edema, lower blood pressure, high blood urea nitrogen, high N-terminal pro-brain natriuretic peptide, anemia, and lack of beta-blocker prescription are independently associated with mortality and re-hospitalization.[9] Fluid and electrolyte hemostasis are integral components of HF. Serum sodium (Na) is the focus of discussion as a recognized marker of adverse outcomes in patients with HF. However, this long-debated pro-Na view has been challenged by many recent research studies.[10] Recently, it has been observed that low serum chloride (Cl) levels (hypochloremia) on admission can predict mortality risk in HF. Surprisingly, survival analysis studies using Na and Cl have proposed a stronger prognostic value for serum Cl levels.[10,11]

In this SANRA-compliant review, we reviewed the role of serum Cl as a potential prognostic marker of HF. We also explored the possible mechanisms of the Cl interactions in HF and their impact on the outcome.

2. Search methods

We carried out a comprehensive review of the literature electronically. The keywords used were HF, serum Cl, hypochloremia, electrolytes, mortality, and certain Boolean searches. The authors investigated PubMed, Google Scholar, EBSCO, and Biomed Central databases from August 02, 2022, to August 06, 2022. We searched for studies published in the past 10 years in the English language only, including randomized controlled trials, systematic reviews, meta-analyses, observational studies, and review articles. Cross-references from relevant studies were employed. We identified a minimal number of studies from all sources. The search for articles using the Medical Subject Headings (MeSH) terms "Heart Failure," "Electrolytes," "Sodium iodide," and "Mortality" yielded no results in PubMed.

3. Serum Cl and the pathophysiology of HF

Cl is usually tested in combination with other electrolytes in cases of cardiac failure. Although there is no agreement regarding the normal serum Cl level ranges, hypochloremia and hyperchloremia are often defined as <96 mmol/L and >105 mmol/L, respectively. Electrolytes are essential for intracellular signaling in cardiac myocytes and contribute to cellular action potentials in the cardiovascular system. Cl channels in the heart affect the membrane potential and action potential duration in the sinoatrial node, which can cause arrhythmias. This arrhythmogenesis results from abnormal Cl levels, which are partly mediated by dysregulated myocyte intracellular pH and potassium (K) levels, and can lead to sudden cardiac death.[12]

Patients with HF demonstrate a more than 50% decrease in the presence of a Cl transfer regulator called the cystic fibrosis transmembrane conductance regulator in an adaptive mechanism during the HF progression.[13] Consequently, this may lead to instability in repolarization and a higher tendency for cardiac arrhythmias. Moreover, this electrolyte imbalance causes dysregulation of myocyte intracellular pH, which carries the risk of arrhythmias. The adaptive remodeling of Cl channels can contribute to the progression of myocardial hypertrophy and subsequent HF.[12-14]

4. Studies of Cl abnormalities in HF

In a Chinese retrospective study comprising large amounts of data from two registries (N = 4,762 and N = 3,481), hypochloremia was present in 10.2% and 20.1% of the study population, respectively. Further, after adjusting for confounders, hypochloremia was associated with mortality in HF (90-day mortality: Adjusted hazard ratio [aHR]: 1.69; 95% CI: 1.27 – 2.25; P < 0.001 in one population, and 1.36 [1.17 – 1.59]; P < 0.001 in the second population). The same study also found hypochloremia as a predictor of long-term mortality (aHR: 1.26; 95% CI: 1.06 – 1.50; P = 0.009, and 1.48 [1.32 – 1.66]; P < 0.001), respectively.[14] A study of patients with acute decompensated HF (ADHF) admitted

to the Cleveland Clinic from July 2008 to December 2013 also documented Cl changes. Hypochloremia was found in 10.7% of the HF patients, 12.6% of those with HFrEF, and 9.3% of individuals with HFpEF. They reported that Cl levels independently predicted long-term mortality during hospitalization, and both were inversely associated (hazard ratio [HR], 0.94; 95% CI: 0.92 – 0.95; $P < 0.001$). This study demonstrated that even after multivariate risk adjustment, serum Cl was significantly associated with mortality in ADHF (HR, 0.93; 95% CI: 0.90 – 0.97; $P < 0.001$).[15,16]

Another study of 39,298 hospitalized patients from 2009 – 2013 compared serum Cl levels at admission and at least twice during hospitalization and its effects on in-hospital death. Of the total patients, 59% had normal Cl levels throughout hospitalization, 21% had hospital-acquired hypochloremia, 15% developed hyperchloremia, and 5% had both abnormalities. Their mortality was associated with hyperchloremia (odds ratio [OR]: 2.84; $P < 0.001$) and both hyper- and hypochloremia (OR: 1.72; $P = 0.004$). Hypochloremia alone was not significantly associated with in-hospital mortality (OR: 0.91; $P = 0.54$). This study showed that nearly half of hospitalized patients had serum Cl abnormalities. It was concluded that hyperchloremia, rather than hypochloremia, was associated with high mortality.[17] The relationship between hypochloremia and hyponatremia and their effects on mortality was demonstrated in a prospective and single-center observational study. At the 3-month follow-up, 45% of adult patients with acute HF (AHF) and hypochloremia on admission developed hyponatremia at 3 months, and only 3% without baseline hypochloremia developed hyponatremia. Hypochloremia at admission was significantly associated with hyponatremia after 3 months ($P < 0.001$; OR: 27.08; 95% CI: 4.3 – 170.7). It was observed that patients who had low Cl and normal Na at admission exhibited statistically significantly higher in-hospital mortality (OR: 4.08; CI: 1.08 – 15.43; $P = 0.039$).[18]

A cohort study of 1996 individuals from December 2016 to June 2019 showed that the prevalence of hypochloremia was 26.1% (521/1996) in patients with HF. It shows that serum Cl levels at admission have an independent and inverse association with all-cause mortality in HF (HR: 0.967; 95% CI: 0.939 – 0.996; $P = 0.026$) as compared to Na, which after multivariable adjustment was no longer significant ($P > 0.05$).[19] A study of ADHF subjects shows that low serum Cl (hypochloremia) predicts the risk of cardiac death at discharge, irrespective of the EF. It shows that hypochloremic individuals had a significant risk of cardiac death as compared to those without it in the HFrEF (HR: 3.38 [1.03 – 11.08], $P = 0.007$), HEmrEF (HR: 4.37 [1.20–15.[9], $P = 0.025$), and HFpEF (HR: 3.13 [1.01 – 9.74], $P = 0.048$) groups.[20]

The results of the above studies provide the basis that when dealing with HF patients, it is important to look at and monitor Cl levels as essentially as Na. However, these studies have limitations that should be interpreted judiciously. Most studies were either prospective or retrospective cohort or registry-based studies. None of these studies was a randomized controlled trial or interventional study. However, all the studies reported data from a significant number of patients. Further, most studies report similar outcomes, which makes these findings worth examining.

5. Intracellular electrolytes in HF

Several compensatory mechanisms are activated in chronic HF (CHF), which affect the metabolism of electrolytes. Activation of the renin-angiotensin-aldosterone (RAAS) system causes Na retention and loss of K and magnesium. The secondary hyperaldosteronism may lead to high intracellular Na and low intracellular K through the cell membrane permeability effect. Magnesium deficiency may further increase intracellular Na and decrease intracellular K, as Mg is a mandatory ion for the Na-K pump.[21]

6. Mechanisms of Cl interaction in HF

6.1. Cl and blood pressure

Some studies suggest that high dietary Na does not increase blood pressure without Cl. An old study from 1929 described that the Cl component raised blood pressure because Na salts of bicarbonate (HCO_3) did not elicit the equivalent pressor effect as did NaCl in hypertensive subjects. Furthermore, in those with hypertension, dietary K reduced blood pressure in the form of KCl compared to potassium citrate ($K_3C_6H_5O_7$). However, there is little scientific evidence that the accompanying Cl anion is necessary to determine the pressor effect of NaCl. NA salts of $C_6H_5O_7$, HCO_3, and PO_4 do not appear to affect the rise in blood pressure.[22,23]

6.2. Physiology of Cl

Cl is the most abundant extracellular and intracellular anion, accounting for 70% of total negative ions. Due to its high concentration, Cl is essential for maintaining electroneutrality. Cl contributes about 100 out of 300 mOsm/L of ECF tonicity.[23] Volume-homeostasis-regulating mechanisms generally activate through changes in the Na and Cl levels. There is a negative relationship between Cl and HCO_3, which maintains the acid-base balance through reciprocal transport in and out of RBCs and renal tubules.[23] Cl clearance is a crucial pathway in the renal adaptation of metabolic acidosis and chronic respiratory acid-base disorders. The gut and kidneys mainly regulate circulating Cl levels in the body. Cl is absorbed across the entire length of the intestine and secreted in the form of HCl from parietal stomach cells.[23,24]

The osmotic gradient between the gut lumen and mucosa is what causes fluid to be secreted into the intestinal tract, and it is mainly caused by Cl and, to a lesser degree, HCO_3 ions. Under normal circumstances, the kidneys regulate the daily dietary intake of NaCl. The entire length of human kidney nephrons expresses Cl channels, which take part in transepithelial transport, acidification of intracellular vesicles, and cell volume regulation. The macula densa in the juxtaglomerular part of the kidney mainly uses Cl instead of Na to sense salt and volume status. When the volume is normal, there is less salt reabsorption in the proximal tubule, with more NaCl reaching the macula. This adequate NaCl sensed at the macula, in turn, inhibits renin secretion and blocks RAAS. This effect is independent of Na; however, the effect does not occur when the macula is exposed to NA bicarbonate ($NaHCO_3$) instead of NaCl. This neurohormonal mechanism suggests that Cl is mainly responsible for renin and volume status regulation, supporting the Cl theory.[23-25]

HF causes decreased cardiac output and, hence, reduces renal blood flow. Low renal perfusion triggers a compensatory alteration of renal arteriolar resistance, along with renal salt and water retention, to maintain plasma volume. Notably, activation of the RAAS, non-osmotic vasopressin release, and increased sympathetic nervous tone in individuals with HF aid in this process (Figure 1). Moreover, renal beta-adrenergic receptors seem to play an essential role in the initiation and maintenance of renal compensatory mechanisms.[26]

Kidneys are the key organs in HF-related congestion and volume overload. They are the main organs affected by hypoperfusion and are the sites of primary counter-regulatory responses. Moreover, the kidneys are a target of prolonged diuretic therapy in patients with cardiac and renal disorders. However, the long-term use of diuretics results in decreased responsiveness and further renal deterioration in the form of diuretic resistance.[26]

7. Diuretic resistance

There is no consensus in the literature among clinicians regarding the definition of diuretic resistance. However, it is agreed that the decreased diuretic and natriuretic effects of loop diuretics worsen fluid overload. Diuretic resistance affects 25 – 30% of patients with HF and causes fluid retention despite higher doses of loop diuretics.[26,27] Many physiological alterations in CHF can cause changes in drug pharmacokinetics, such as problems in drug absorption, distribution, metabolism, and excretion of diuretics. However, these changes alone do not explain the diuretic resistance observed in HF.[28,29] Patients with CHF, when compared to healthy subjects, have a decreased drug absorption rate, which causes a delay in achieving a threshold drug dose with the resultant diuretic resistance. Surprisingly, the bioavailability of diuretics remains the same, which explains these changes, preferably due to gut edema in HF.[29,30]

In general, loop diuretics reach the renal tubular fluid through secretion from an organic anion transport channel

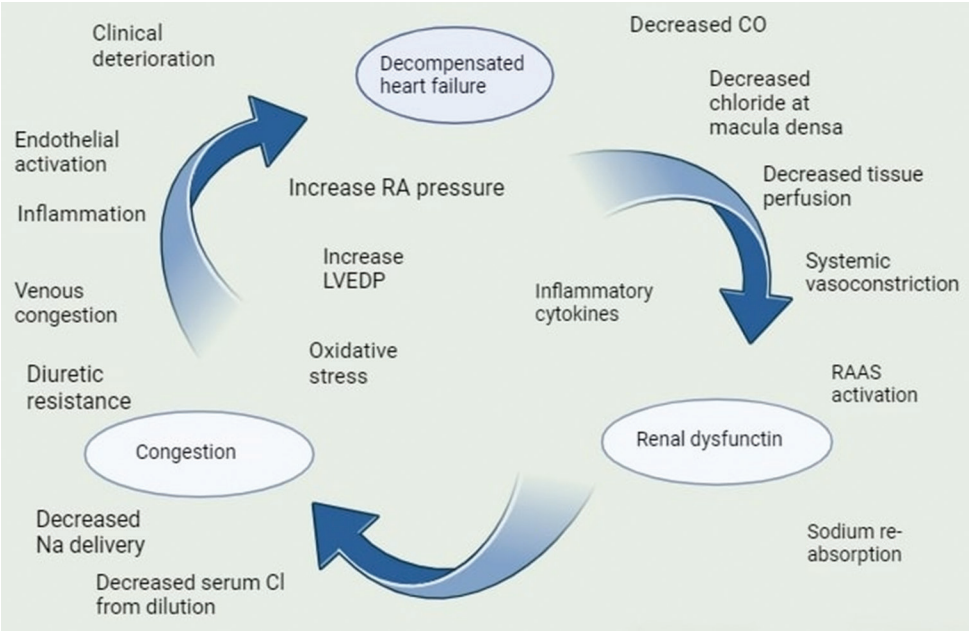

Figure 1. Interplay of pathophysiologic mechanisms in HF. Image created using BioRender.com.
Abbreviations: CO: Cardiac output; LVEDP: Left ventricular end-diastolic pressure; RA: Right atrial; RAAS: Renin angiotensin aldosterone system.

in the proximal renal tubule.[31] In HF, renal insufficiency causes diuretic resistance due to inadequate tubular diuretic concentrations, which is due to reduced renal perfusion and impaired proximal tubular secretion.[29-32] Furthermore, secretion of diuretics is decreased due to endogenous organic anion accumulation, which competes with loop diuretics such as furosemide at the receptors on the organic anion transporter.[33] Therefore, higher doses of loop diuretics are necessary to counter this competitive inhibition and achieve therapeutic urinary concentrations in individuals with CHF with renal impairment. In general, abrupt administration of diuretics, especially loop diuretics in healthy individuals, can activate the RAAS reflexively, which, in turn, causes additional salt and water retention and makes diuretic therapy less effective.[34]

There are several possible mechanisms proposed for diuretic resistance in patients with HF. However, the mechanisms that cause Na retention and altered loop diuretic pharmacokinetics theories are the most widely accepted and discussed. A decrease in renal blood flow limits diuretic delivery to the kidneys, coupled with low eGFR, which reduces tubular Na delivery. Both of these mechanisms can play a role in diuretic resistance. Loop diuretics block reabsorption at the macula densa in the loop of Henle, which causes vasoconstriction of the afferent arteriole through the tubule-glomerular feedback mechanism. This inhibition of tubule-glomerular feedback with loop diuretics should enhance renal blood flow and GFR. However, aggressive use of diuretics in diuretic-resistant HF may raise serum creatinine levels in these patients.[35]

7.1. Role of Cl in salt sensing

It has been proposed that Cl is the primary ion involved in the renal ability to sense volume overload in AHF. This is because only Cl-containing solutions elicit a renal response compared to non-Cl solutions.[36] Studies have shown that Cl also reduces renin release from the kidneys, an effect not observed with non-Cl salts. Therefore, Cl has a significant role in the response to volume overload, regulation of fluid status, and RAAS activation, both of which are disturbed in the setting of AHF. Newer studies explain the relationship between serum Cl and diuretic targets. It was observed that hypochloremic individuals had higher renin levels than non-hypochloremic individuals.[36,37]

7.2. New concepts in Cl metabolism

Recent studies suggest the role of with-no-lysine kinases (WNKs). These are serine-threonine kinases in the distal convoluted tubules that normally phosphorylate and activate many kinases that further activate the Na-K-2Cl and Na-Cl cotransporters (NKCC and NCC). In this way, WNKs cause the upregulation of Na-K-2Cl cotransporters (Figure 2), which leads to Na and water reabsorption.[38] The discovery that Cl directly inhibits these WNKs provided a molecular phenomenon that links Cl to the WNK pathway and Cl transport.[39] Many recent studies have reported that WNKs sense low Cl levels in the body. Once Cl is bound to the active site on WNKs, autophosphorylation is inhibited, and Na-K-2Cl cotransporters and Na-Cl cotransporters are reduced. This causes a decrease in renal Na levels and water reabsorption. The activities of both loop and thiazide diuretics are regulated by Cl.[37-39] There is a different tubule-glomerular response to different classes of diuretics, with loop diuretics altering it whereas others do not. The blockade of the Na-potassium Cl cotransporter reduces the reabsorption of Na and water. This leads to the depletion of ECF volume and subsequent neurohormonal activation.

8. HF treatment and hypochloremia

8.1. Restriction of salt

The dietary intake of salt, most commonly NaCl, affects the concentration of serum electrolytes. Although there is limited evidence that salt or fluid restriction improves volume overload in patients with CHF, the HF treatment guidelines still use this strategy for symptomatic relief.[40] However, the detrimental effects of salt restriction are focused on, possibly due to the further activation of neurohormonal mechanisms and HF progression. This activation may be due to hypochloremia, hyponatremia, or both. There is no established evidence that low dietary salt intake reduces electrolyte levels. Furthermore, the clinical effect of salt restriction in patients with HF has not yet been established.[41]

8.2. HF pharmacotherapy

There is no clear evidence that diuretic therapy offers mortality benefits in patients with HF. Diuretics are the main therapy for treating volume overload and symptomatic relief from congestion.[41,42] This phenomenon results in free water retention and increased hypochloremia. Loop diuretics can increase the excretion of Cl by 20-fold. There is more Cl loss with loop diuretics as compared to Na and K.[43] The Na-K-2Cl pump in the thick ascending limb allows Na reabsorption in the distal nephron, leading to reduced hyponatremia with loop diuretics. However, Cl reabsorption is distally limited. Thiazide diuretics inhibit Na-Cl channels in the distal tubule, causing both hypochloremia and hyponatremia.[44] Moreover, when combined with salt restriction, loop diuretics may further reduce tubular delivery and reabsorption of Cl and worsen hypochloremia in this setting.[45,46]

Mineralocorticoid receptor antagonist (MRA) therapy may not improve hypochloremia but can prevent a further decrease in Cl concentration in HF. There is no evidence

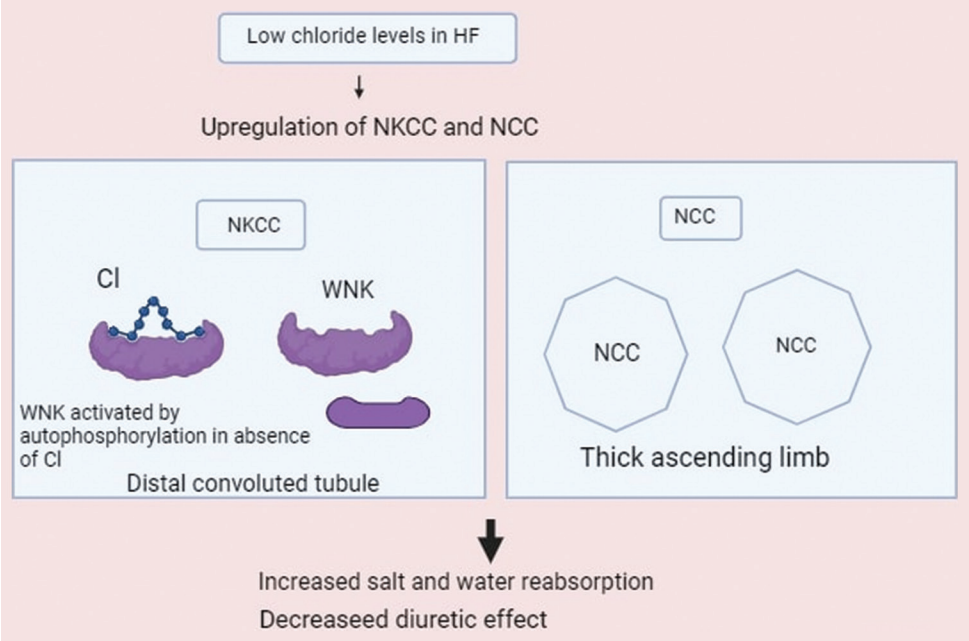

Figure 2. Hypochloromia-induced diuretic resistance and function of with-no-lysine kinases. Image created using BioRender.com. Abbreviations: Cl: Chloride; HF: Heart failure; NCC: Na-Cl cotransporter; NKCC: Na-K-2Cl cotransporter.

that MRA therapy causes a decrease in Cl levels.[47,48] Acetazolamide, the carbonic anhydrase inhibitor, increases the concentration of Cl and decreases serum HCO_3 irrespective of serum Na. It inhibits the intracellular and luminal enzyme carbonic anhydrase in the renal proximal tubule. There is no evidence for the effect of treatment with angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and beta-blockers on serum Cl metabolism.[49,50]

8.3. Hyperchloremia

Hyperchloremia is typically observed in critically ill patients under intensive care. Research identifies that hyperchloremia is more prevalent in subjects with acute kidney injury, sepsis, and in those admitted to surgical ICUs. Unlike hypochloremia, hyperchloremia is less prevalent in HF. It is usually iatrogenic in origin due to over-replacement or loss of excessive hypotonic fluids rather than the disease process.[51]

8.4. Treatment of hypochloremia

Hypochloremia was recently established as an important marker of HF prognosis and raised the question of diuretic resistance. Therefore, Cl homeostasis is essential for the clinical determination and treatment of HF, if necessary.[52] In the background of the "Chloride Theory" of HF, serum Cl manipulation can be an important therapeutic target. An alternative diuretic choice may be beneficial. The addition of a carbonic anhydrase inhibitor diuretic can be an appropriate therapy to regain Cl in refractory HF.[53,54] Acetazolamide exhibits a unique and critical mechanism of action. It acts as a non-absorbable anion, which causes the excretion of HCO_3 in the renal tubules, exchangeable absorption of Cl into the blood, and simultaneous urinary excretion of K.[55] Several studies explain the potent effect of this class of diuretics in specific HF situations complicated with low serum Cl and metabolic alkalosis, which follows the treatment with loop diuretics in the form of refractory HF.[52,55,56]

Moreover, MRA agents are recommended for the treatment of HF, but they are usually underprescribed and withdrawn due to hyperkalemia. However, there is no risk of hypochloremia associated with the use of these agents. In such conditions, the use of acetazolamide, due to its K-lowering properties, can make the use of MRA possible.[57] The correction of hypokalemia with these agents can be achieved by increasing the dose of MRA agents or K supplementation to prevent malignant ventricular arrhythmias.[45,58] In light of these observations, the addition of acetazolamide, with or without MRA agents, to loop diuretics in patients with refractory HF is a promising treatment option.

8.5. A potential therapeutic target

Low serum Cl levels in HF and critically ill patients are associated with mortality and organ dysfunction.[52,59,60] The results from a cohort study of critically ill patients described that both low and high serum Cl levels were associated with acute kidney injury.[60] More recently, two large randomized

controlled trials (SALTED and SMART) observed the beneficial effects of balanced solutions over 0.9% saline in reducing major adverse kidney events (MAKE). They reported that less critically ill adults developed MAKE in a balanced solution group compared to those treated with 0.9% saline fluid.[61,62]

9. Conclusion

This review explains that serum Cl disturbances, in particular hypochloremia, are common in patients with HF. It also shows that low Cl levels are associated with mortality, frequent hospitalization, and worsening of HF in these patients. There is evidence that only the Na-centric view of electrolytes in HF should not be used in managing HF populations. We observed that the underlying pathophysiology of hypochloremia in HF should be considered when managing this group of patients. Furthermore, there is a need to look for diuretic resistance and its potential treatment with agents beyond loop diuretics. In instances of hypochloremia and other potential pathways, the administration of loop diuretics can lead to the development of diuretic resistance and suboptimal outcomes in conditions characterized by excessive fluid volume. When managing congestive symptoms associated with HF, it is imperative to explore a range of diuretic therapeutic options due to the presence of hypochloremia, diuretic resistance, and additional electrolyte irregularities. Studies have also demonstrated that salt restriction may cause hypochloremia and worsen this condition. Therefore, it is essential to determine standard levels of Cl in the serum and urine for direct treatment. In addition, further research should be conducted on the possible functions of WNKs and alternative pathways as new therapeutic targets. There is a need for large-scale studies, mainly randomized controlled trials, and studies that focus on dietary interventions to strengthen the evidence of these results and recommend future practice guidelines.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Shafaat Raza
Writing—original draft: All Authors
Writing—review & editing: All Authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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ACCSCIENCE PUBLISHING

Brain & Heart

PERSPECTIVE ARTICLE

Pictorial rendition of author's observations on balloon valvuloplasty/angioplasty procedures: Pulmonary stenosis

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Abstract

Balloon valvuloplasty/angioplasty techniques have been available to address valvar and vascular obstructions associated with congenital heart defects (CHDs) since the 1980s. The objective of this paper is to provide a pictorial rendition of the author's observations over the last four decades on these techniques. In this paper, balloon pulmonary valvuloplasty (BPV) for treating isolated pulmonary stenosis (PS), PS associated with cyanotic CHDs, and bioprosthetic valve in the pulmonary position were reviewed. Balloon dilatation leads to a decrease in the peak systolic pressure gradient through the pulmonary valve during BPV, as well as at intermediate-term and long-term evaluation. Problems, such as the reappearance of obstruction at intermediate-term follow-up and pulmonary insufficiency (PI) at long-term follow-up, have been documented in isolated PS cases but are infrequent. Repeat balloon valvuloplasty for restenosis has been successfully used. The development of infundibular obstruction in PS cases was also reviewed. To decrease the frequency and degree of PI, the author has revised the recommendations for balloon/annulus ratios used for BPV from the previous 1.2 – 1.4 to 1.2 – 1.25. In patients with PS associated with cyanotic CHD, improvement of oxygen saturations at the time of BPV and enhanced anatomy during follow-up were observed. BPV of bioprosthetic valves results in minimal improvement in the pulmonary valve gradient, and stents may be a better alternative to address this problem.

Keywords: Balloon pulmonary valvuloplasty; Restenosis; Pulmonary insufficiency; Infundibular stenosis; Long-term follow-up results; Cyanotic heart defects; Bioprosthetic valves

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Citation: Rao PS. Pictorial rendition of author's observations on balloon valvuloplasty/angioplasty procedures: Pulmonary stenosis. *Brain & Heart*. 2024;2(1):2406. https://doi.org/10.36922/bh.2406

Received: December 12, 2023

Accepted: January 23, 2024

Published Online: February 15, 2024

1. Introduction

In 1964, Dotter and Judkins performed dilatation of peripheral arteries with progressively increasing sizes of guidewires and catheters, resulting in favorable outcomes.[1] Dotter and Judkins' principle was later extended by Grüntzig *et al.*, who created catheters with double-lumen and non-flexible balloons to effectively dilate stenotic peripheral, renal, and coronary arterial lesions.[2-5] Grüntzig's balloons were utilized by Kan *et al.*,[6] Singer *et al.*,[7] Sperling *et al.*,[8] and Lababidi[9] to alleviate congenital cardiac narrowing of the valves and blood vessels in children. In 1966, Rashkind and Miller introduced balloon atrial septostomy to promote blood mixing at the atrial level in babies with transposed great

vessels.[10] In 1967, Porstmann *et al.* described percutaneous occlusion of patent ductus arteriosus (PDA).[11] Shortly thereafter, Rashkind and Cuaso developed different PDA occluding devices.[12] In 1976, King *et al.* introduced a device to close atrial septal defects (ASDs).[13] Subsequently, Rashkind and Cuaso designed a different ASD occluding device.[14] In 1964, Dotter and Judkins proposed the concept of stents.[1] The introduction of the spiral coil-spring device by Dotter[15] and stainless steel mesh stents by Palmaz *et al.*[16] followed. The author utilized these devices and subsequently developed transcatheter techniques during his academic practice over the last four decades. Prospective data collection before the procedure and during follow-up was secured with appropriate Food and Drug Administration and local institutional review board approvals as per the requirements of that time. The objective of this paper is to present a pictorial rendition of the author's observations on balloon valvuloplasty/angioplasty procedures, transcatheter occlusion practices, and stent implantation techniques. Due to the voluminous amount of material, the presentation is divided into multiple parts. This paper, which constitutes the first part of the series, reviews balloon pulmonary valvuloplasty (BPV) of pulmonary stenosis (PS). Subsequent papers discuss other balloon valvuloplasty/angioplasty procedures, transcatheter occlusion techniques, and stent implantations.

2. Isolated stenosis of the pulmonary valve

Grüntzig's technique[2-5] was employed by Kan *et al.* in the early 1980s to dilate stenotic pulmonary valves.[6] Eventually, BPV became the procedure of choice to address pulmonary valve stenosis.[17] The indications for BPV are similar to those used for surgical valvotomy, specifically pulmonary valve peak systolic pressure gradients higher than 50 mmHg.[18] In this section, the technique and results of BPV to treat valvar PS are reviewed.

2.1. BPV techniques

Examples of BPV techniques are presented in Figures 1-3.

2.2. Immediate results

Rao[19] evaluated the immediate outcomes of BPV in the mid-1980s. Subsequently, the immediate outcomes of a higher number of patients[21] were investigated, revealing a reduction in pulmonary valve peak-to-peak systolic pressure gradients and peak systolic pressures in the right ventricle (RV) following BPV. There was also a slight increase in pressures in the pulmonary artery (Figures 4 and 5); however, the cardiac index remained unchanged.[19] The narrow jet of contrast across the stenotic pulmonary valve remarkably increased following BPV (Figure 6). The dimension of the RV became smaller

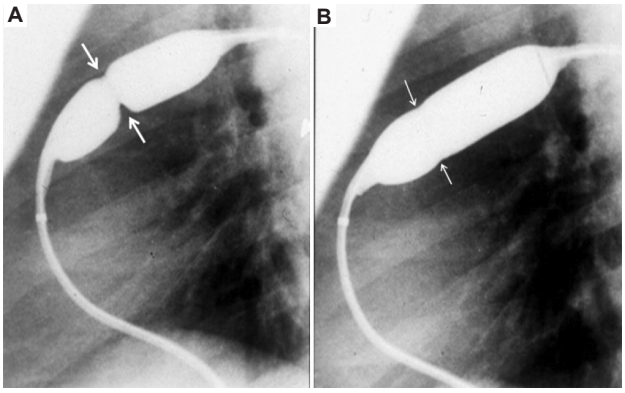

Figure 1. The procedure of balloon pulmonary valvuloplasty involves the placement of a balloon valvuloplasty catheter through the stenotic pulmonary valve and inflating it with diluted contrast material. (A) Balloon waisting is observed as the balloon is inflated (arrows), a result of the narrowed pulmonary valve. (B) Disappearance of the waisting (arrows) is observed as the balloon is further inflated, leading to the relief of pulmonary valve obstruction. Only lateral views are shown. Modified from Rao.[19]

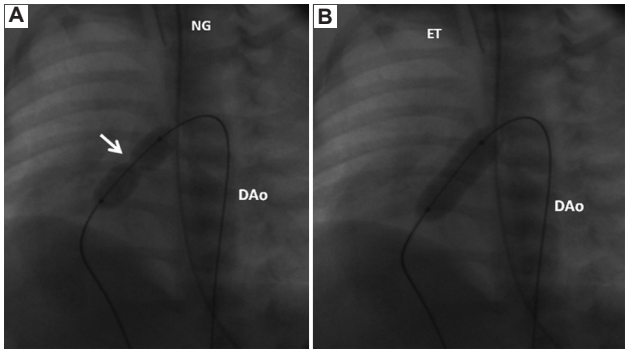

Figure 2. (A) Balloon waisting in a neonate. (B) The waisting is eliminated as the balloon is inflated. The radiograms are recorded in a sitting-up view. Descending aorta (DAo), endotracheal tube (ET), and nasogastric tube (NG) are labeled. Adopted from Rao *et al.*[20]

(Figure 7). Reviewing angiograms and echocardiograms following BPV revealed free excursion of the leaflets of the pulmonary valve with a reduction of pulmonary valve doming. In patients with right atrium-to-left atrium shunting via an atrial defect before BPV, the atrial shunt disappeared or reversed (Figure 8) following successful BPV. However, some patients developed RV infundibular stenosis, which will be reviewed in the next section. Most patients no longer required surgery, and with the exception of neonates, all patients were discharged on the day following the BPV procedure.[17,19,21] The immediate outcomes of BPV documented by other cardiologists[22-42] during the 5-year period (1982 – 1987) following the initial description of BPV aligned with the Rao,[17] Rao,[19] and Rao *et al.*'s[21] observations. More recent studies of BPV performed between 2007 and 2020, published in

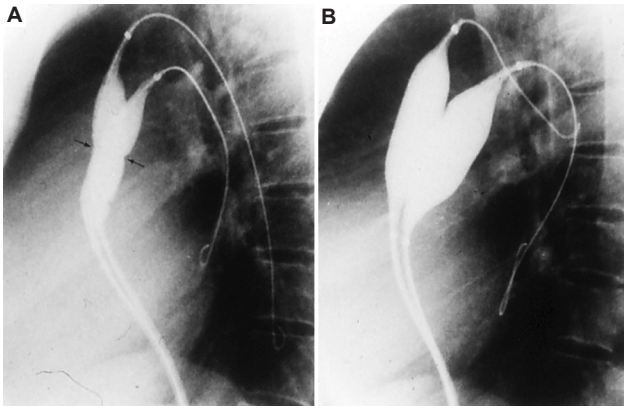

Figure 3. In patients with a pulmonary valve annulus that is too big to be dilated with one balloon, two balloons may be positioned through the pulmonary valve to perform balloon dilatation. (A) The waisting of the balloons (arrows) and (B) their disappearance. Since large-diameter balloons are now available, it is rarely necessary to use a double-balloon technique at the present time. Reproduced from Rao.[19]

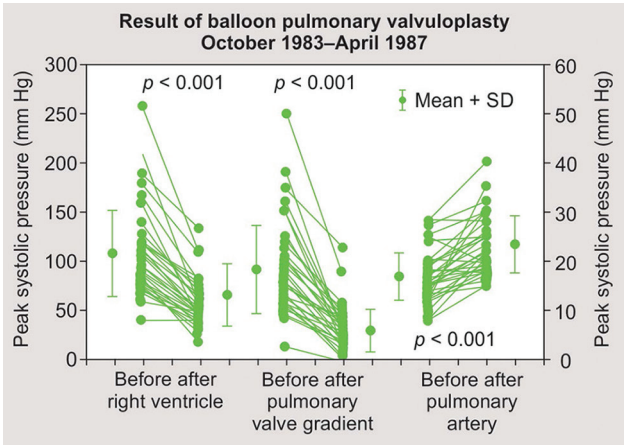

Figure 4. The acute outcomes of balloon dilatation of the pulmonary valve are shown in a line graph format. Note the decrease in pulmonary valve gradients (middle line graph) and peak systolic pressures in the right ventricle (left line graph) following balloon pulmonary valvuloplasty ($P < 0.001$). In addition, a mild elevation in pulmonary artery pressures (right line graph) is observed.
Abbreviation: SD: Standard deviation. Adopted from Rao.[48]

2020 through 2024,[43-47] showed outcomes similar to those described above.

2.3. Development of the right ventricular infundibular stenosis

Thapar and Rao,[50] as well as Fontes *et al.*,[51] investigated the incidence and importance of RV infundibular narrowing following BPV. The author and colleagues analyzed the outcomes of 62 BPV patients, while Fontes scrutinized 33 patients with severe PS. RV infundibular obstruction is observed more frequently in older patients and those with more severe degrees of obstruction. Most infundibular

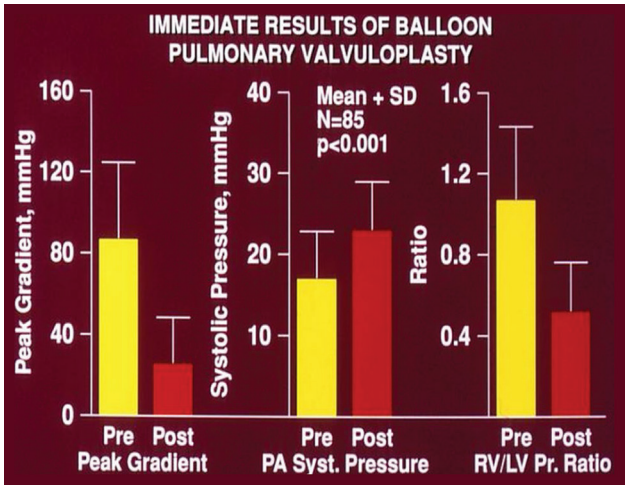

Figure 5. Graph depicting the acute outcomes of balloon dilatation of the pulmonary valve (PV) in a larger cohort of children ($N = 85$). The graph shows a reduction in gradients across the PV (left bar graph) and a decrease in the ratio of the right (RV) and left (LV) ventricular systolic pressures (Pr) (right bar graph), which is another measure of successful balloon pulmonary valvuloplasty (BPV). There is a slight increase in peak pressures in the pulmonary artery (PA) (middle bar graph).
Notes: N: Number of patients; Pre: Before BPV; Post: Immediately after BPV; SD: Standard deviation. Adopted from Rao.[49]

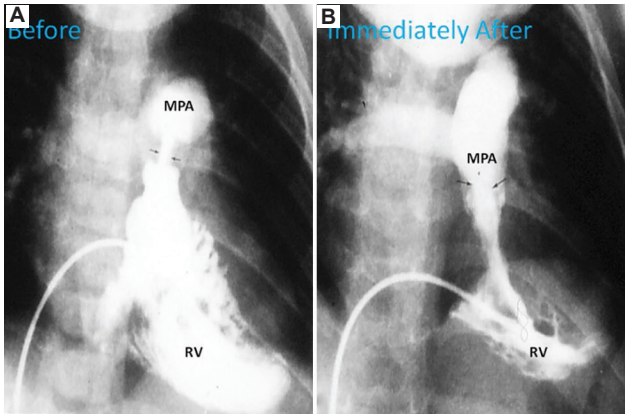

Figure 6. A cineangiogram of the right ventricular performed before balloon pulmonary valvuloplasty (BPV) demonstrates (A) a narrow jet of contrast (arrows), which (B) remarkably increased following BPV (arrows). Both cineangiograms were obtained in sitting-up views. The main pulmonary artery (MPA) is labeled. Adopted from Rao.[19]

obstructions were found to resolve (Figure 9) after successful BPV in both studies. Such improvement can be demonstrated both by angiography (Figure 10) and by Doppler echocardiography (Figure 11). Infundibular obstructions with gradients ≥50 mmHg are treated with beta-blocker therapy,[50,51] with rare instances requiring surgery.

2.4. Intermediate-term results

At intermediate-term follow-up, the peak-to-peak pulmonary valve pressure gradients remained lower

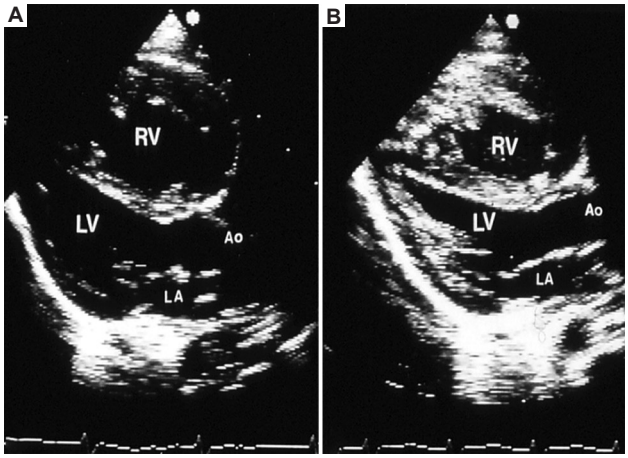

Figure 7. A two-dimensional echocardiogram performed before balloon pulmonary valve dilatation demonstrates (A) a dilated right ventricle (RV). Following successful balloon pulmonary valve dilatation, the RV size decreased (B).
Abbreviations: Ao: Aorta; LA: Left atrium; LV: Left ventricle. Adopted from Rao.[49]

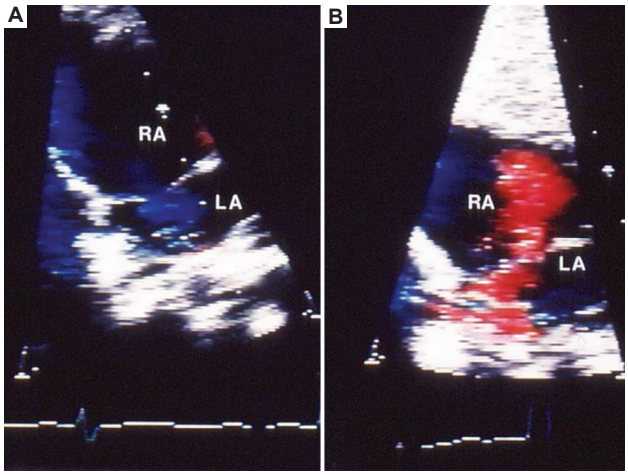

Figure 8. In patients who have shunting from the right atrium (RA) to the left atrium (LA) via an atrial septal defect (A) before balloon pulmonary valvuloplasty (BPV), the atrial shunt disappears or reverses (B) following successful BPV. Adopted from Rao.[48]

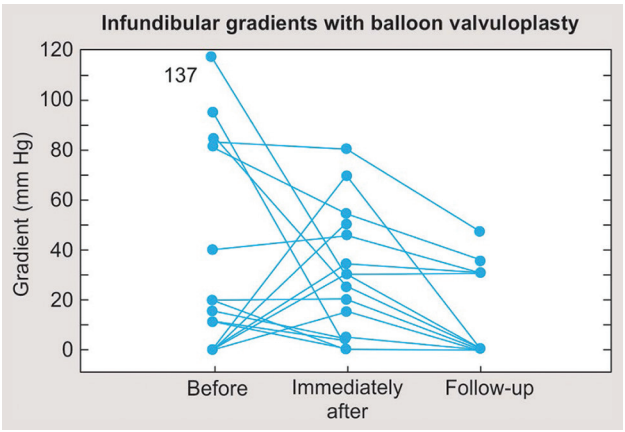

Figure 9. Infundibular obstruction may be present before balloon pulmonary valvuloplasty (BPV), may appear immediately after BPV, and/or at follow-up. The graph above shows pressure gradients across the right ventricular infundibulum and how they progress. Such obstructions are prevalent in older patients with more severe degrees of obstruction.[45,46] Most infundibular obstructions resolve after successful BPV, as illustrated in this graph and observed in angiographic (Figure 10) and Doppler (Figure 11) examinations. Infundibular obstructions with gradients ≥50 mmHg are treated with beta-blocker medications, with surgery being a rare necessity.[45,46] Modified from Thapar and Rao.[50]

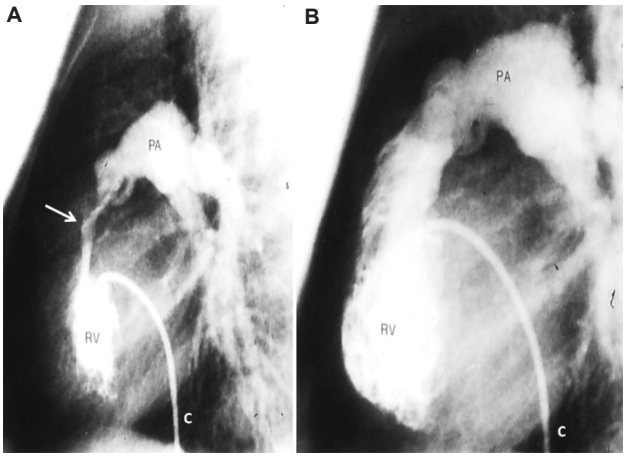

Figure 10. Cineangiographic images demonstrating right ventricular (RV) infundibular stenosis that developed after balloon pulmonary valvuloplasty (A) which resolved at a follow-up study 10 months later (B). The pulmonary artery (PA) is labeled. Adopted from Thapar and Rao.[50]

than pre-BPV gradients without remarkable variation when compared to immediate post-BPV gradients. This reduction in the gradients was demonstrated by both cardiac catheterization (Figure 12) and Doppler studies (Figures 13 and 14).[21] Initially, cardiac catheterization was used to assess the results of BPV. Once Doppler studies were shown to accurately reflect transvalvar gradients,[52] echo-Doppler studies were utilized for this assessment. The cardiac diameter on a chest roentgenogram (Figure 15), the function of the RV, the extent of tricuspid regurgitation (Figure 16), and the RV infundibular narrowing (Figures 10 and 11) showed improvement at intermediate-term follow-up.[21] There was only a minimal increase in the degree of pulmonary insufficiency (PI) at intermediate-term follow-up.[21] The intermediate-term follow-up results of BPV recorded by other interventionalists during the 5-year period (1982 – 1987) after the first description of BPV are similar[22-42] to what Rao,[19] Rao *et al.*[21] have observed. Intermediate-term outcomes were also similar in early 2000.[44,47] Recurrence of PS is observed in nearly 10% of patients[53] and will be reviewed in the next section.

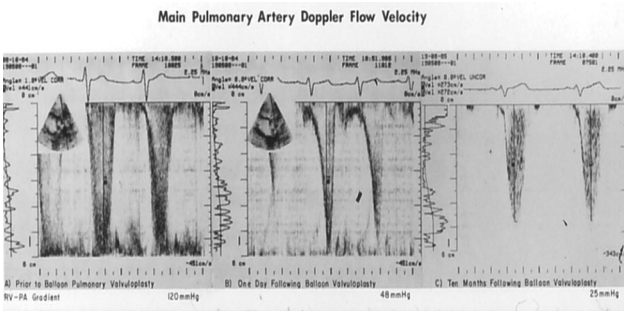

Figure 11. Doppler studies conducted before balloon pulmonary valvuloplasty (BPV) (left panel), the day after BPV (middle panel, corresponding to Figure 10A), and at the 10-month follow-up study (right panel, corresponding to Figure 10B). Note the triangular-shaped Doppler signal in the middle panel, suggesting infundibular obstruction, which disappeared on follow-up (right panel). Reproduced from Thapar and Rao.[50]

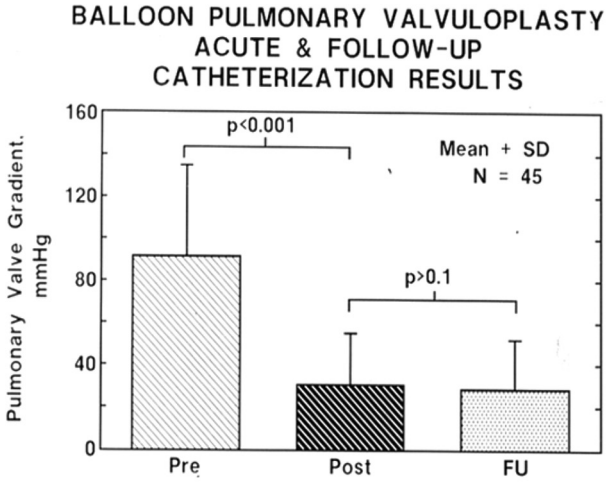

Figure 12. Initially, follow-up (FU) outcomes of balloon pulmonary valvuloplasty (BPV) were assessed by repeat cardiac catheterization. The data on 45 patients showed that the peak pulmonary valve pressure gradient in systole both immediately after BPV (Post) and at intermediate-term FU were lower than those measured before BPV (Pre) ($P < 0.001$). The gradients at FU are similar ($P > 0.1$) to those of immediate post-BPV values.
Notes: N: Number; SD: Standard deviation. Adopted from Rao.[19]

2.5. Development of restenosis and causes of restenosis

While the outcomes of BPV for the entire cohort are favorable, as exemplified in Figures 12 and 13, restenosis, defined as a peak systolic pulmonary valve gradient in excess of 50 mmHg, occurred in nearly 10% of patients when scrutinizing the outcomes of each child[53] (Figure 17). To investigate the causes of restenosis, the follow-up outcomes of BPV of 36 patients were divided into two groups: Group I with good results ($N = 29$) and Group II with poor outcomes ($N = 7$).[53] Low-pressure gradients across the

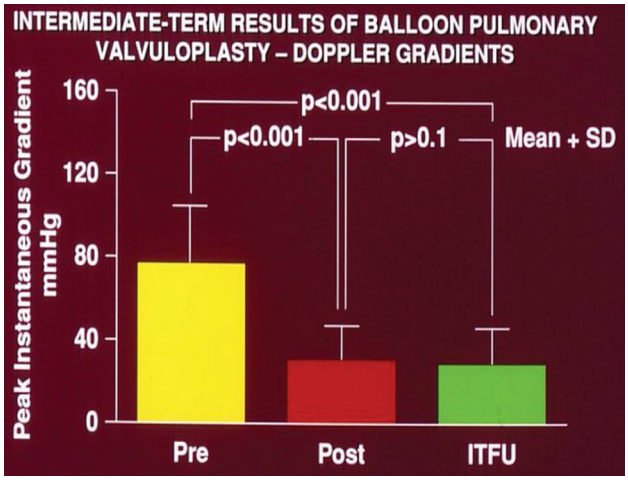

Figure 13. Similar to Figure 12, follow-up outcomes of balloon pulmonary valvuloplasty (BPV) were initially assessed by repeat cardiac catheterization. After the demonstration of the accuracy of peak instantaneous Doppler gradients in predicting catheterization-measured gradients,[52] Doppler data were used for this assessment. This bar graph demonstrates a reduction ($P < 0.001$) in pulmonary valve peak Doppler pressure gradients at intermediate-term follow-up (ITFU) after BPV.
Notes: Pre: Before BPV; Post: The day following BPV; SD: Standard deviation. Modified from Rao.[21]

pulmonary valve were observed both immediately after BPV and at follow-up in Group I patients (Figure 18, left panel). In Group II (children with poor outcomes), there was a decrease ($P < 0.05$) in pulmonary valve pressure gradients immediately after BPV, but at follow-up, the gradients returned to values similar to those of pre-BPV ($P > 0.1$) (Figure 18, right panel). Fourteen biographical, pathologic, physiological, and procedural factors were analyzed using multivariate logistic regression.[53] This examination identified balloon/annulus (B/A) ratio <1.2 and post-BPV peak-to-peak pressure gradients across the pulmonary valve higher than 30 mmHg[53] as causes of restenosis (Figures 19 and 20). Based on these data, Rao *et al.*[53] conclusions were that restenosis is related to the use of a B/A ratio ≤1.2, and the reappearance of stenosis may be anticipated by immediate post-BPV transpulmonary valve pressure gradients exceeding 30 mmHg. In a subsequent investigation,[21] evaluating the long-term results of 80 patients, the risk factors for recurrence were exactly the same as those observed in Rao *et al.*'s[53] initial study.

2.6. Feasibility and effectiveness of repeat balloon pulmonary valvuloplasty

As mentioned in Section 2.5, which discusses the development of restenosis and causes of restenosis, and Figures 17 and 18, restenosis was observed following BPV. Ten out of 80 patients developed restenosis.[21,54] These patients underwent repeat BPV to relieve recurrent stenosis. In this group of patients,

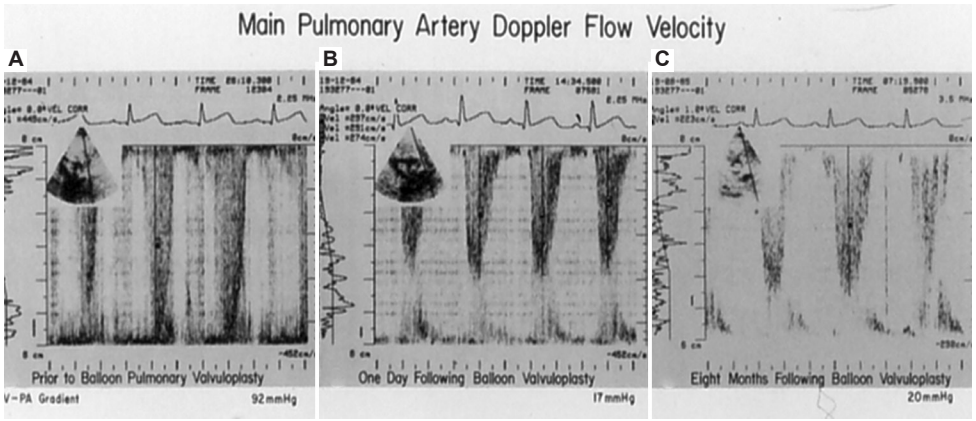

Figure 14. Examples of Doppler studies before (A), the next day following (B), and 8 months following (C) balloon pulmonary valvuloplasty (BPV) demonstrating a reduction in Doppler peak instantaneous gradient from 92 mmHg (A) to 17 mmHg on the day after (B) and to 20 mmHg 8 months (C) after BPV. Reproduced from Rao.[52]

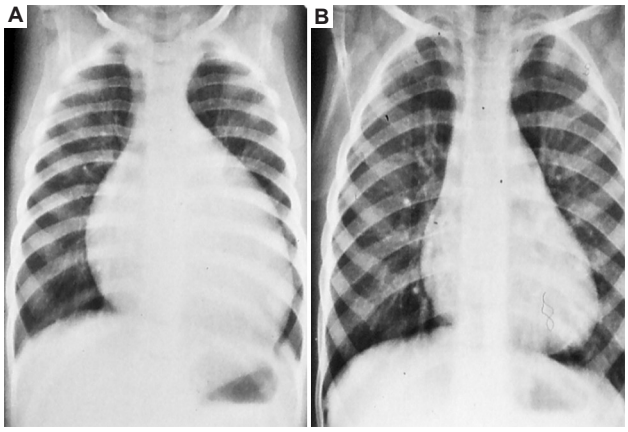

Figure 15. Chest roentgenograms obtained before (A) and at intermediate-term follow-up (B) after balloon pulmonary valvuloplasty demonstrate a decrease in the diameter of the cardiac silhouette. Adopted from Rao.[19]

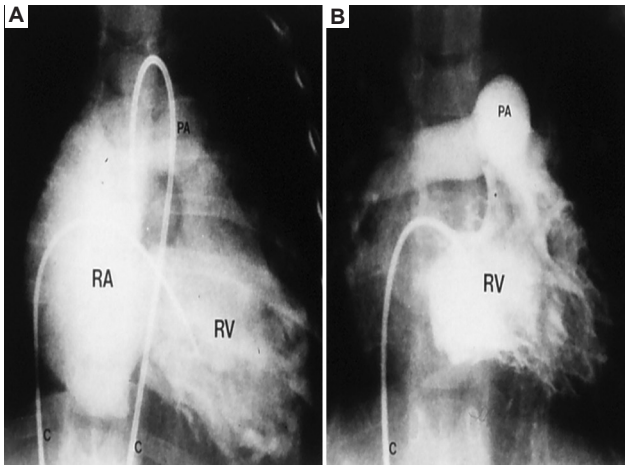

Figure 16. Cineangiograms of the right ventricle (RV) captured before (A) and at intermediate-term follow-up (B) after balloon pulmonary valvuloplasty demonstrate the total resolution of tricuspid valve regurgitation. The pulmonary artery (PA) and right atrium (RA) are labeled. Adopted from Rao.[19]

the pulmonary valve gradients decreased (98 ± 45 mmHg vs. 46 ± 33 mmHg; $P < 0.05$) following the first BPV (Figure 21). These patients were restudied 11 months (on average) later; the pulmonary valve gradients increased (89 ± 40 mmHg; $P < 0.05$) and were similar ($P > 0.1$) to pre-BPV values. Subsequent repeat BPV resulted in a significant reduction ($P < 0.01$) of pulmonary valve gradients from 89 ± 40 mmHg to 38 ± 20 mmHg ($P < 0.01$). Doppler studies conducted 2 – 6½ years following repeat BPV showed excellent findings with residual Doppler-derived gradients of 24 ± 13 mmHg (Figure 21). Based on these observations, it may be inferred that repeating BPV is useful and valuable in relieving recurrent narrowing of the pulmonary valve.[54]

2.7. Single- versus double-BPV

The double-balloon method (Figure 3) was employed for BPV before the availability of balloons with large diameters in patients with an annulus of the pulmonary valve too big to be dilated with one balloon. When the double-balloon method is utilized, the effective balloon diameter may be determined by Equation I:

$$\text{Effective balloon diameter} = 0.82\ (D1 + D2) \qquad (I)$$

Where D1 and D2 represent balloon diameters used during BPV. The formula to compute the effective diameter of both balloons together was developed by Rao[55] and later simplified by Narang *et al.*[56] Some cardiologists advocated the use of the double-balloon technique, particularly in adult patients.[57] Therefore, Rao and Fawzy[58] investigated whether the double-balloon method is superior to using one balloon for BPV. As demonstrated in Figure 22, both immediate and follow-up outcomes of the two-balloon and one-balloon methods of BPV were excellent ($P < 0.001$) and similar ($P > 0.1$). The B/A ratios used for both

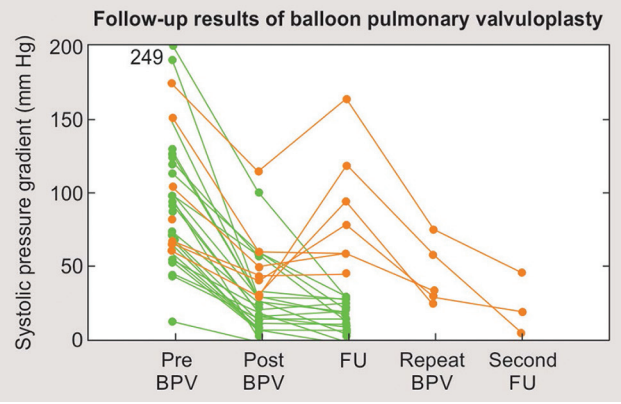

Figure 17. The line graph depicts the good-result group (green lines) and the poor-result group (orange lines). Results of the second BPV are also displayed for the patients with restenosis. The causes of restenosis are examined in Figures 18 and 19. Reproduced from Rao.[48]
Abbreviations: BPV: Balloon pulmonary valvuloplasty; FU: Follow-up.

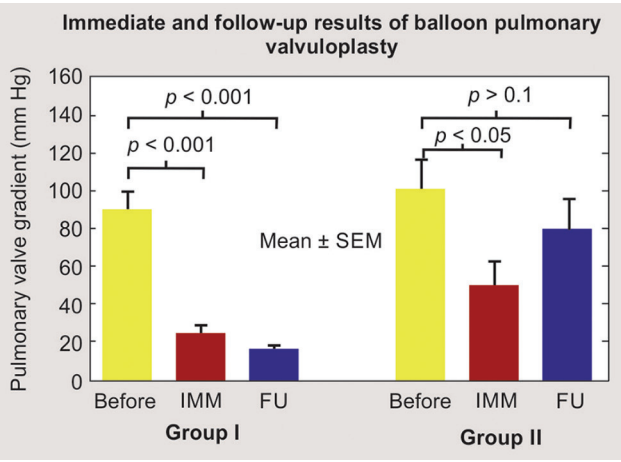

Figure 18. The bar graph demonstrates low-pressure gradients across the pulmonary valve in Group I both immediately (IMM) after BPV and at follow-up. In group II (children with poor outcomes), there is a decrease ($P < 0.05$) in the pulmonary valve pressure gradient IMM after BPV, but at follow-up (FU), the gradient returned to values similar ($P > 0.01$) to pre-BPV values. Adopted from Rao.[48]

techniques, RV systolic pressures and pulmonary valve gradients before BPV (Figure 23), immediately after BPV, and at follow-up (Figure 24) were also similar ($P > 0.1$) for both techniques. It was concluded that the outcome of the two-balloon method is excellent but not superior to the one-balloon technique. The two-balloon technique may be employed if the annulus of the pulmonary valve is too big to dilate with commercially accessible balloon catheters.[58]

2.8. Effect of balloon diameters on the outcomes of BPV

Rao,[19] Rao *et al.*,[53] Rao,[55] Rao and Fawzy,[58] Rao,[59] Rao[60] conducted a comprehensive investigation into the effect of

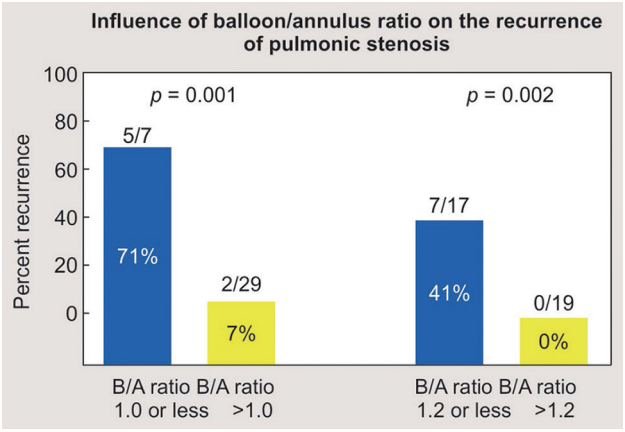

Figure 19. This graph demonstrates the role of the balloon-to-pulmonary valve annulus ratios on the frequency of restenosis after balloon pulmonary valvuloplasty; the lower the balloon/annulus (B/A) ratio, the higher the recurrence rate ($P = 0.001 – 0.002$). The actual number of patients is indicated at the top of the bars, while the percentages are shown within the bars. Adopted from Rao.[48]

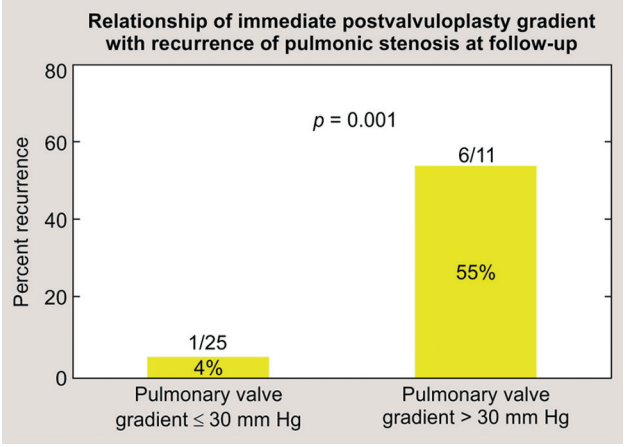

Figure 20. This graph demonstrates the impact of residual pressure gradients across the pulmonary valve after balloon pulmonary valvuloplasty on the frequency of restenosis; the higher the residual pulmonary valve gradients, the higher the recurrence rate ($P = 0.001$). The actual number of children is indicated at the top of the bars, while the percentages are shown within the bars. Reproduced from Rao.[48]

B/A ratios on the outcomes of BPV. The key findings from these investigations are as follows: (i) B/A ratios <1.2 are associated with restenosis in nearly 10% of patients; (ii) B/A ratios exceeding 1.4 offer no additional benefits beyond the range of 1.2 – 1.4 and may potentially harm the pulmonary valve apparatus;[61] and (iii) B/A ratios within the range of 1.2 – 1.4 are deemed most appropriate for achieving successful relief of pulmonary valvar stenosis following BPV.[19,53,55,58-60] Figures 18-20 and 25-29 present the data supporting these conclusions. While the recommendation for B/A ratios of 1.2 – 1.4 for BPV has remained steady for the next decade and a half, a downward revision was prompted by the

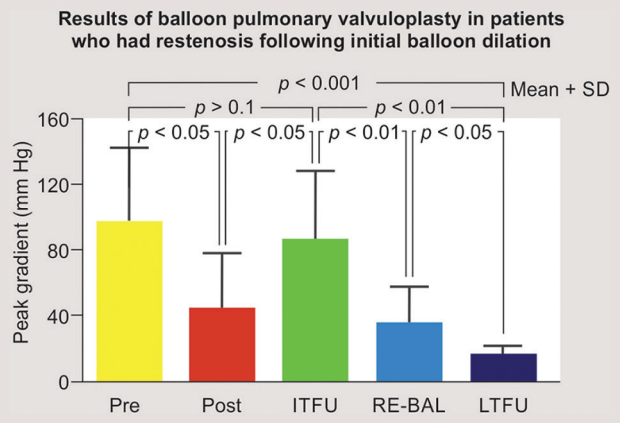

Figure 21. This bar graph shows the results of repeat balloon pulmonary valvuloplasty (BPV) in patients who experienced restenosis following the first BPV. The transvalvar gradients were 98 ± 45 mmHg before (Pre) the first BPV, which were significantly reduced ($P < 0.05$) after BPV (Post). Follow-up data at intermediate-term (ITFU) revealed that the peak pulmonary valve gradients returned to levels similar to those before BPV ($P > 0.1$). Upon repeat BPV (RE-BAL), the transvalvar gradients decreased significantly ($P < 0.01$), with an additional reduction ($P < 0.05$) observed at long-term follow-up (LTFU). These data indicate that repeating BPV to address restenosis is feasible, safe, and effective.[49]
Abbreviation: SD: Standard deviation. Adopted from Rao *et al.*[54]

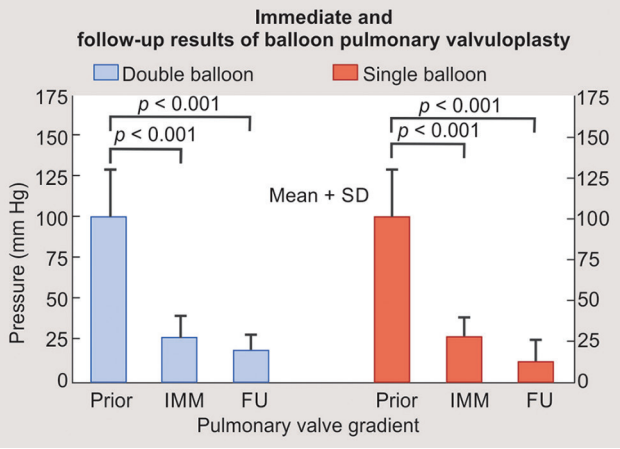

Figure 22. The bar graph shows both immediate (IMM) and follow-up (FU) outcomes of the two-balloon (double balloon) and one-balloon (single balloon) methods of balloon pulmonary valvuloplasty (BPV). Using both techniques, the IMM ($P < 0.001$) and FU ($P < 0.001$) results were excellent, showing a reduction of peak-to-peak pressure gradients across the pulmonary valve.[53] Figures 23 and 24 illustrate additional comparisons between both groups.
Notes: Prior: Before BPV; SD: Standard deviation. Amended from Reference.[58]

development of PI at long-term follow-up, a topic that will be further discussed in Section 2.10 of this paper.

2.9. Electrocardiographic changes

The author and colleagues investigated the occurrence of electrocardiographic (ECG) changes after BPV and

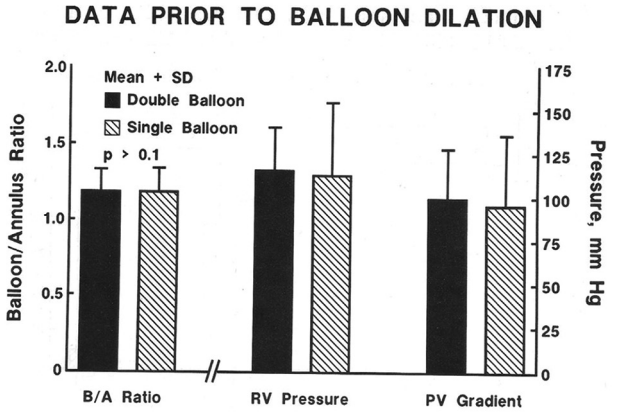

Figure 23. Comparison of balloon/annulus (B/A) ratios (left group) used for balloon pulmonary valvuloplasty (BPV) in both double- and single-balloon techniques; these were similar ($P > 0.1$). The peak systolic pressures in the right ventricle (RV) (middle group) and peak systolic pressure gradients across the pulmonary valve (PV) (right group) were also comparable ($P > 0.1$) for double- and single-balloon groups.
Abbreviation: SD: Standard deviation. Reproduced from Rao and Fawzy.[58]

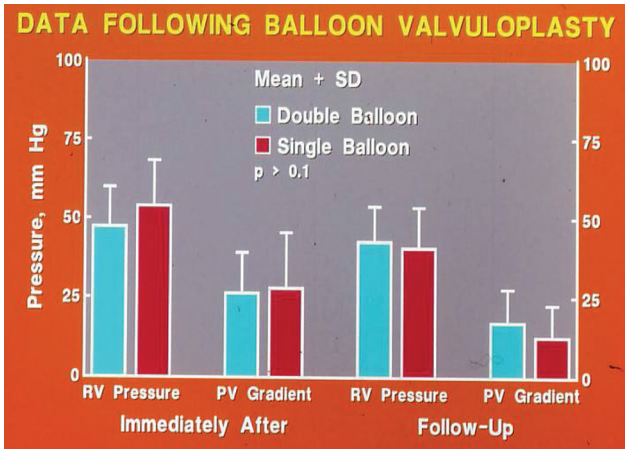

Figure 24. The comparisons between the peak systolic pressures in the right ventricle (RV) and peak systolic pressure gradients across the pulmonary valve (PV) show similarity ($P > 0.1$) for both double- and single-balloon groups immediately after balloon pulmonary valvuloplasty (BPV). Similarly, these values remained comparable ($P > 0.1$) at follow-up evaluation. These data suggest that both single- and double-balloon techniques provide similar relief of pulmonary valve obstruction, provided that the balloon/annulus ratios are similar.[58]
Abbreviation: SD: Standard deviation. Amended from Rao and Fawzy.[58]

assessed whether these ECGs reflected improved peak-to-peak systolic pressure gradients across the pulmonary valve. Among the 35 patients with both pre-BPV and follow-up data, 30 children exhibited favorable results (Group I), defined by follow-up residual gradients across the pulmonary valve <50 mmHg. Group II consisted of five children who exhibited poor outcomes at follow-up with gradients exceeding 50 mmHg.[62] The data, as depicted in Figures 30 and 31, suggest that the ECGs were

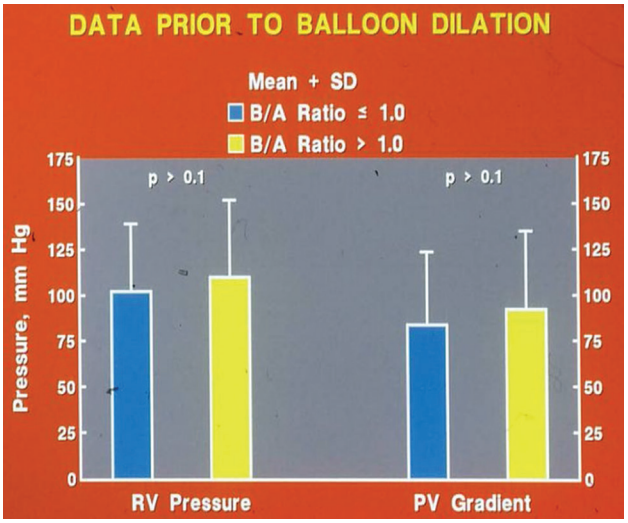

Figure 25. The right ventricular (RV) peak systolic pressures and pulmonary valve (PV) peak-to-peak systolic pressure gradients in the group with a balloon/annulus (B/A) ratio ≤1.0 (blue bars) are similar ($P > 0.1$) to those in the group with a B/A ratio >1.0 (yellow bars) before BPV. The data are expressed in mean with standard deviation (SD). These data indicate that the severity of pulmonary valve stenosis was similar in both groups. Reproduced from Rao.[48]

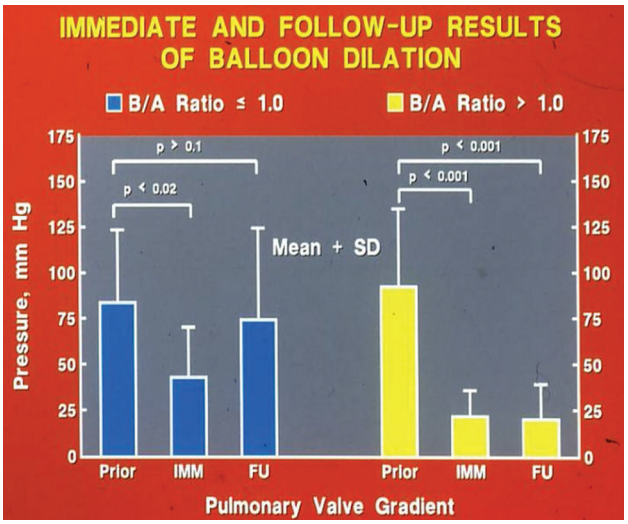

Figure 26. Bar graph illustrating the immediate (IMM) and follow-up (FU) results of balloon dilatation on pulmonary valve peak-to-peak systolic pressure gradients. In the group with a balloon/annulus (B/A) ratio ≤1.0 (blue bars), there was a significant decrease ($P < 0.02$) in the pulmonary valve gradient immediately after balloon valvuloplasty; however, follow-up (FU) results showed that these values had reverted toward pre-dilatation levels ($P > 0.1$). In the group with a B/A ratio >1.0 (yellow bars), a decrease ($P < 0.001$) in the pulmonary valve gradient was observed both immediately after balloon valvuloplasty and at FU. The data are expressed in mean with standard deviation (SD). Modified from Rao.[60]

similar in both groups before BPV.[62] Following BPV, both frontal plane and horizontal plane mean QRS vectors

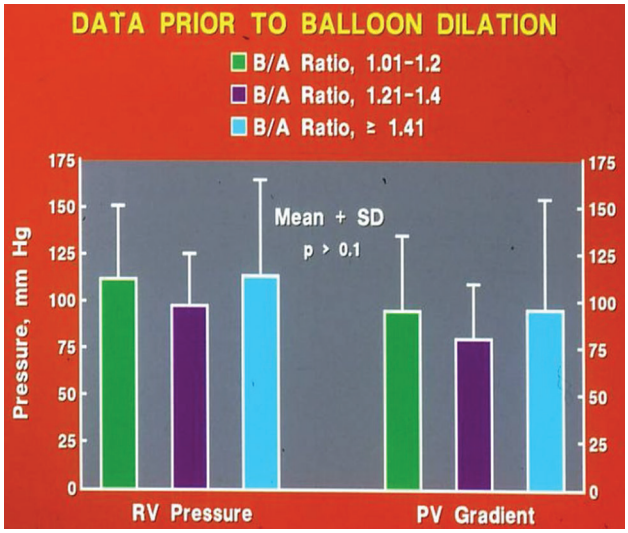

Figure 27. The right ventricular (RV) peak systolic pressures (left group) and pulmonary valve (PV) peak-to- peak systolic pressure gradients (right group) in the groups with balloon/annulus (B/A) ratios between 1.01 and 1.2 (green bars), B/A ratios between 1.21 and 1.4 (violet bars) and B/A ratios ≥ 1.41 (light blue bars) are shown. The RV peak systolic pressures and PV peak-to-peak systolic pressure gradients are similar ($P > 0.1$) in all three groups. The data are expressed in mean with standard deviation (SD). These data indicate that the severity of pulmonary valve stenosis was similar in all three groups. Modified from Rao.[60]

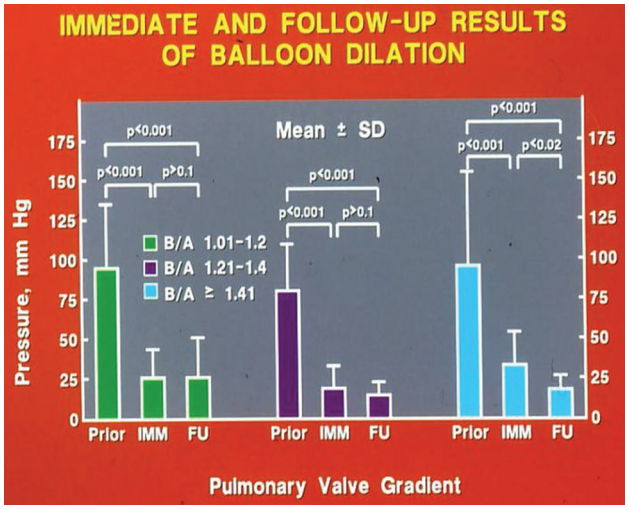

Figure 28. The outcomes of balloon pulmonary valvuloplasty (BPV) with varying balloon/annulus (B/A) ratios. Immediate (IMM) and follow-up (FU) peak-to-peak systolic pressure gradients across the pulmonary valve improved ($P < 0.001$) in all subsets of B/A ratios, suggesting that a BA ratio ≥1.4 has no advantage beyond what was achieved by the other two groups. Abbreviation: SD: standard deviation. Amended from Rao.[60]

shifted leftward ($P < 0.05$) in Group I (Figure 32), while Group II showed no improvement.[62] Right ventricular voltages decreased in Group I children, whereas there was no change in Group II patients (Figure 33). Analyzing the time course of reduction of RV voltages in Group I

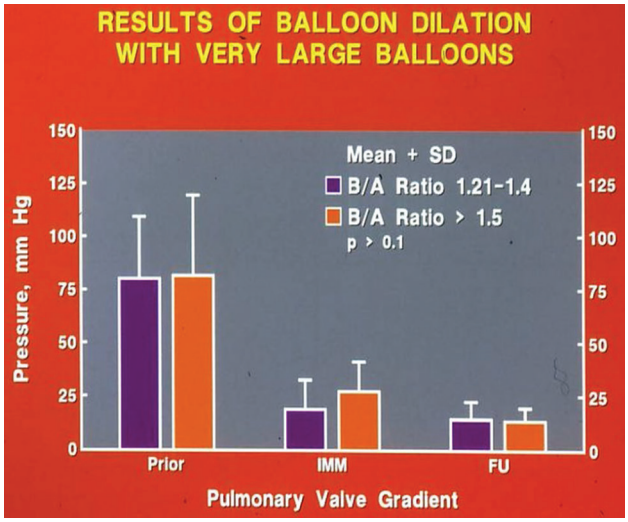

Figure 29. Comparisons of outcomes of balloon pulmonary valvuloplasty (BPV) with balloon/annulus (B/A) ratios of 1.21 – 1.4 versus B/A ratios >1.5. Pulmonary valve gradients before (Prior) (left group), immediately after (IMM) (middle group), and at follow-up (FU) (right group) were similar ($P > 0.1$), suggesting that a BA ratio ≥1.5 has no advantage beyond what was achieved by a B/A ratio of 1.21 – 1.4.
Abbreviation: SD: Standard deviation. Amended from Rao.[60]

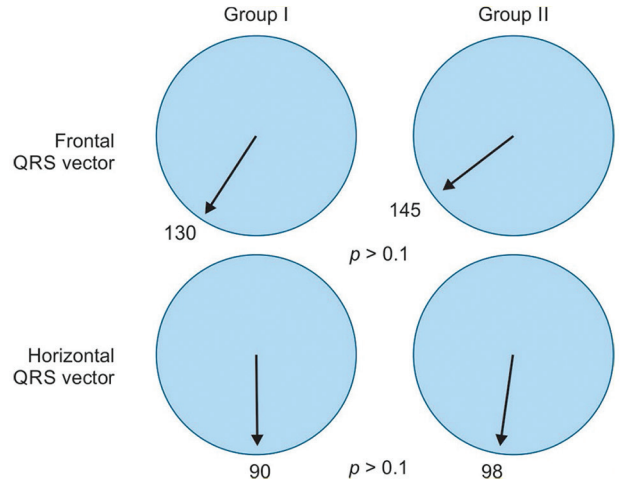

Figure 30. The comparisons between the frontal (upper circles) and horizontal (lower circles) plane mean QRS vectors before BPV show similarity ($P > 0.01$). Reproduced from Rao.[48]

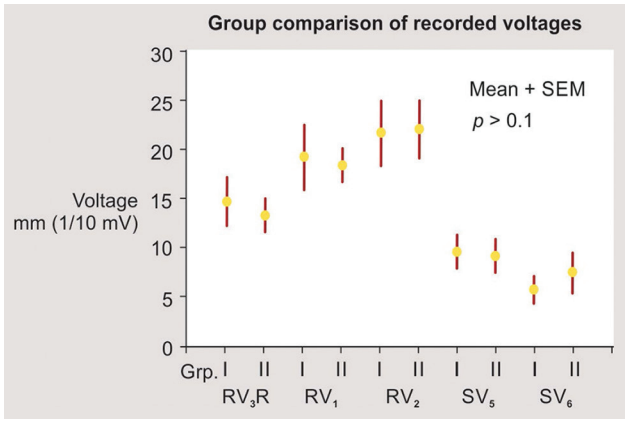

Figure 31. The comparison of precordial voltages between Group (Grp.) I and Grp. II. Right ventricular voltages, reflected by R waves in V3R, V1, and V2, and S waves in V5 and V6, are similar ($P > 0.1$).
Abbreviation: SEM: Standard error. Reproduced from Rao.[48]

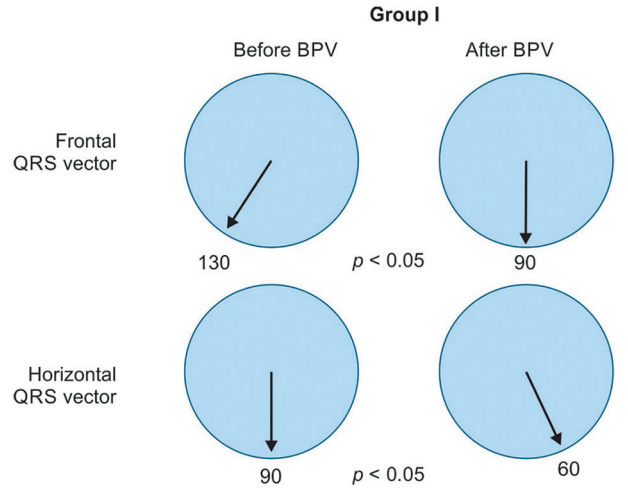

Figure 32. The comparisons between the frontal (top circles) and horizontal (bottom circles) plane mean QRS vectors of Group I children with favorable results. A significant leftward shift ($P < 0.05$) in mean QRS vectors is observed in both frontal and horizontal planes after balloon pulmonary valvuloplasty (BPV). In contrast, a similar comparison of Group II children revealed no significant change ($P > 0.1$) in mean QRS vectors in either the frontal plane (Pre: 145.0 ± 26.5; Post: 145.0 ± 26.5) or horizontal plane (Pre: 98.0 ± 19.2; Post: 112.0 ± 29.3).[57] Reproduced from Rao.[48]

patients revealed no change at 3 months following BPV, but a significant decrease in voltages was observed at 6 and 12 months following BPV (Figure 34). Examining the relationship between post-BPV pulmonary valve gradients and concurrently obtained ECGs revealed a normal ECG in patients with a residual gradient <30 mmHg. The presence of RV hypertrophy (RVH) on ECG indicated either a higher residual pulmonary valve gradient or an ECG obtained within 6 months after BPV (Figure 35). Based on the presented data, Rao and Solymar[62] concluded that ECG findings improve following effective BPV, and ECG is a useful addition in the assessment of results of BPV. However, RVH does not seem to regress until 6 months after BPV.

2.10. Long-term results

Long-term results were evaluated by examining the data from 80 patients who underwent BPV.[21] The follow-up duration varied between 3 and 10 years, with a median of

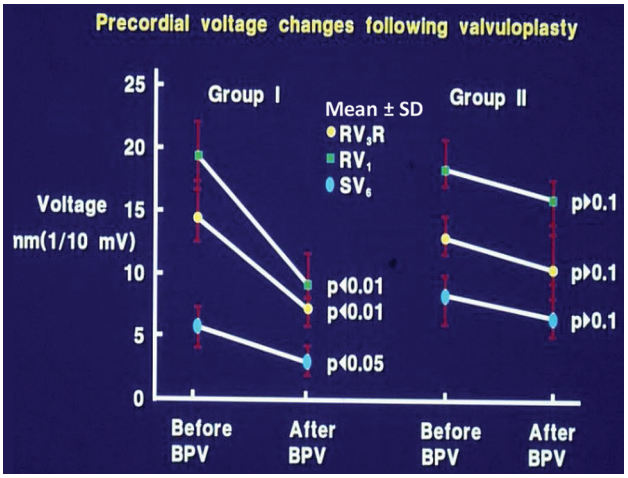

Figure 33. The changes in precordial voltages among patients in Group I and Group II following balloon pulmonary valvuloplasty (BPV). In Group I, there was a significant reduction (P < 0.05 – 0.01) in right ventricular voltages, as reflected by R waves in V3R and V1 and S waves in V6 (left group). Conversely, in Group II patients, there was no substantial change (P > 0.1) (right group).
Abbreviation: SD: Standard deviation. Amended from Rao.[48]

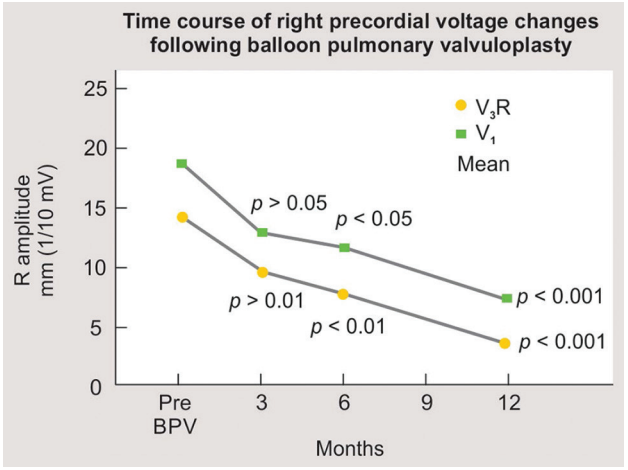

Figure 34. The time course of changes in precordial voltages among Group I patients following balloon pulmonary valvuloplasty (BPV). The right ventricular voltages, as reflected by R waves in V3R and V1, did not show a significant decrease (P > 0.05 – 0.1) in the 3-month follow-up electrocardiogram (ECG). However, ECGs at 6 and 12 months post-BPV demonstrated a significant reduction (P < 0.05 – 0.001) in these voltages. The data are expressed in mean values. Adopted from Rao.[48]

7 years. Parameters such as residual Doppler pulmonary valve gradients, event-free rates (evaluated using the Kaplan-Meyer method[63]), and prevalence of PI were assessed. Doppler data indicated favorable outcomes with low residual gradients for the entire cohort (Figure 36). Actuarial rates, indicating the likelihood of avoiding repeat intervention, were in the mid-to-high 80s at both 5 and 10 years after BPV[21] (Figure 37). However, PI was observed at long-term

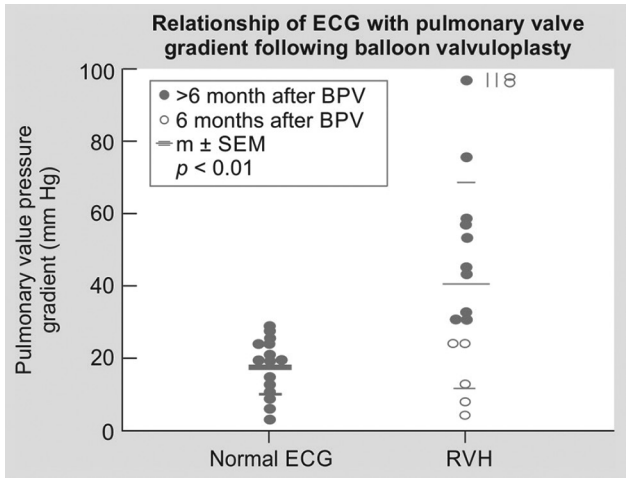

Figure 35. The relationship between post-balloon pulmonary valvuloplasty (BPV) electrocardiograms (ECGs) and post-BPV peak gradients across the pulmonary valve. ECGs appear normal in patients with peak gradients across the pulmonary valve lower than 30 mmHg at follow-up (left group; filled circles). Conversely, hypertrophied right ventricle (RVH) was observed in patients with residual pulmonary valve gradients >30 mmHg (right group; filled circles) or when the ECG was recorded <6 months after BPV (right group; open circles). In the latter group, despite peak gradients across the pulmonary valve being lower than 30 mmHg, it is inferred that RVH does not regress within 6 months following BPV.
Abbreviations: m: Mean; SEM: Standard error of the mean. Reproduced from Rao.[48]

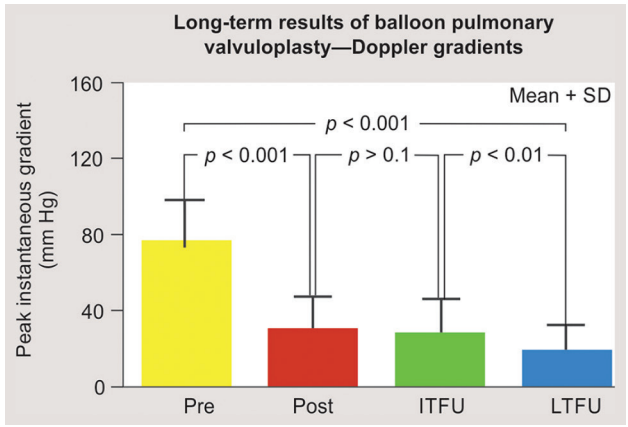

Figure 36. The peak instantaneous Doppler gradients across the pulmonary valve at long-term follow-up (LTFU) were significantly lower (P < 0.001) compared to pre-balloon pulmonary valvuloplasty (BPV) (Pre) measurements. These values remained lower (P < 0.01) than those immediately after BPV (Post) and those at intermediate-term follow-up (ITFU) Doppler gradients. These data indicate successful relief of pulmonary valve obstruction by BPV at LTFU.
Abbreviation: SD: Standard deviation. Amended from Rao *et al.*[21]

follow-up (Figure 38). The method of PI grading is presented in Figure 39.[21] Despite the increased prevalence of PI, there was no evidence of the right ventricular dilatation (Figure 40), with only a minimal increase in the incidence

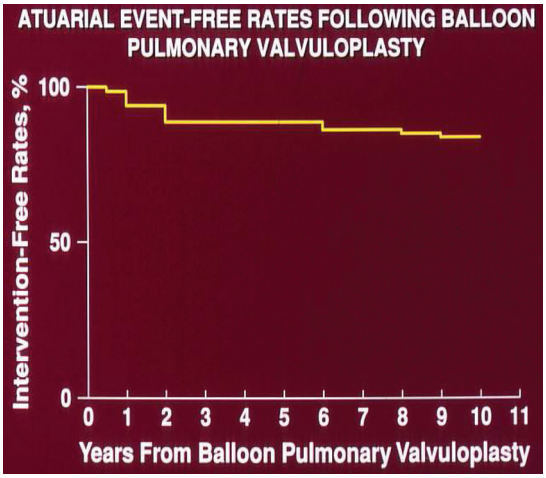

Figure 37. Actuarial event-free levels following balloon pulmonary valvuloplasty (BPV). Out of the total cohort, 10 patients underwent repeat BPV, three required surgery to relieve right ventricular infundibular stenosis, and two patients underwent surgery for supravalvar pulmonary artery stenosis during follow-up. The event-free rates were calculated using the Kaplan-Meyer method.[63] These rates at 5 and 10 years after BPV were in the mid-to-high 80s. Modified from Rao *et al.*[21]

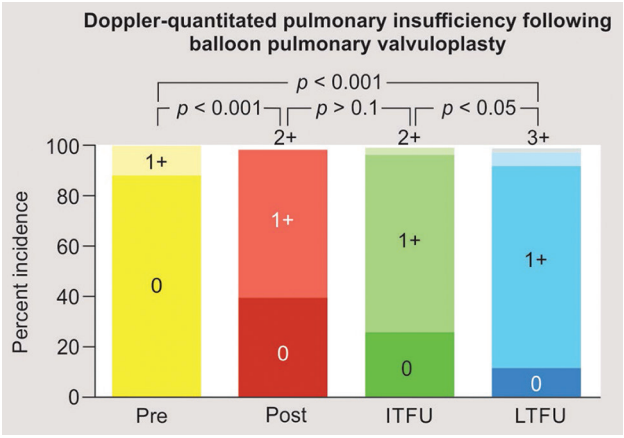

Figure 38. The incidence of pulmonary insufficiency (PI) observed following balloon pulmonary valvuloplasty (BPV). The grading system used is shown in Figure 39.[21] An increase in the degree of PI ($P < 0.001$) occurred following BPV (Pre [before BPV] vs. Post [day after BPV]). At intermediate-term (ITFU), there was no significant change in the degree of PI ($P > 0.1$). However, at long-term follow-up (LTFU), the PI increased when compared with ITFU ($P < 0.05$).[21] Modified from Rao *et al.*[21]

of flat interventricular septal motion (Figure 41). Based on the study, the author and colleagues endorsed BPV as the preferred management for valvar PS, albeit with reservations about the potential adverse effects of PI on long-term follow-up. Rao *et al.*[21] recommended a follow-up evaluation spanning 10 – 20 years to determine the significance of PI. Subsequent to the Rao *et al.*[21] publication, Berman *et al.*[64] reported a significant development of PI requiring pulmonary valve replacement in 6% of their study subjects.

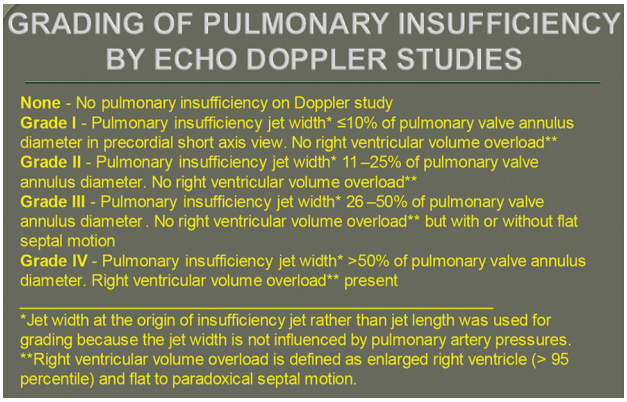

Figure 39. The grading system used in quantifying the degree of pulmonary insufficiency following balloon pulmonary valvuloplasty.[21] Modified from Rao *et al.*[21]

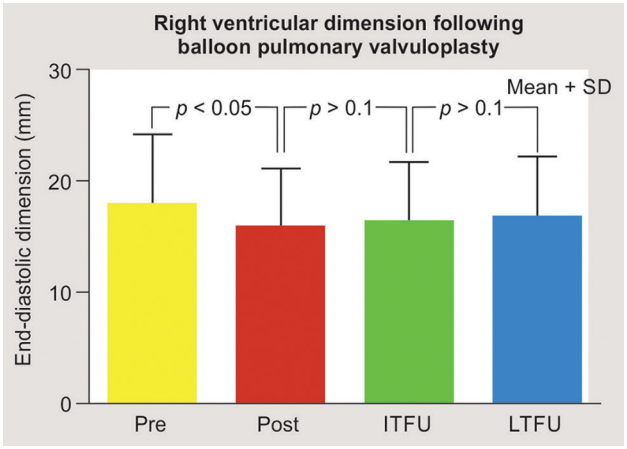

Figure 40. End-diastolic dimensions of the right ventricle before balloon pulmonary valvuloplasty (BPV) (Pre), the day after BPV (Post), and at follow-up at intermediate-term (ITFU), and at long-term (LTFU). The right ventricular dimension decreased ($P < 0.05$) after BPV, while no further increase/decrease ($P > 0.1$) occurred at ITFU and LTFU, signifying no evidence of the right ventricular dilatation at follow-up secondary to pulmonary insufficiency, as described in Figure 38. While not shown in this graph, end-diastolic dimensions of the left ventricle did not alter.[21] Abbreviation: SD: Standard deviation. Modified from Rao *et al.*[21]

In response, the author has revised the recommendations for B/A ratios to be used for BPV from prior 1.2 – 1.4 to 1.2 – 1.25 in an editorial communication,[65] a revision reiterated in subsequent publications.[17,48,49] Several investigations into the causes of the development of PI at long-term follow-up after BPV[64,66,67] have identified a common denominator, a large B/A ratio.[64,66,67] Although it remains unclear whether reducing the B/A ratio will mitigate or eliminate the risk of PI, a recent study by Pathak *et al.*[67] suggested a favorable effect in significantly reducing PI, albeit with a follow-up duration of only 15 months. Long-term follow-up studies are eagerly awaited to confirm these observations.

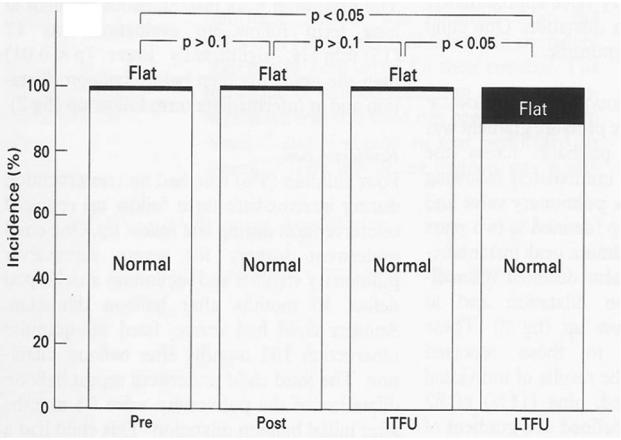

Figure 41. The incidence of abnormalities in interventricular septal motion following balloon pulmonary valvuloplasty (BPV). The prevalence of flat septal motion did not increase ($P > 0.1$) immediately after BPV (Pre vs. Post BPV), nor did it increase ($P > 0.1$) at follow-up intermediate-term (ITFU). However, at follow-up long- term (LTFU), the prevalence of flat septal motion increased ($P < 0.05$), although this was in a small fraction of the total patients. Reproduced from Rao *et al.*[21]

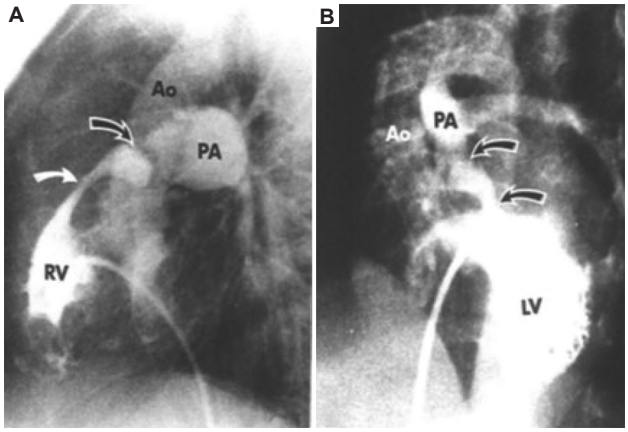

Figure 42. Balloon pulmonary valvuloplasty (BPV) is likely to alleviate pulmonary valve stenosis. In the absence of additional subvalvar or supravalvar obstruction, the pulmonary circuit is subjected to increased pulmonary arterial pressure and flow since most cyanotic heart defects have either a large ventricular septal defect or a single ventricle. To circumvent this problem, there should be two or more obstructions to the pulmonary outflow tract before embarking on BPV for this group of patients.[19,65] The cineangiographic frames above illustrate the presence of subvalvar stenosis (filled white arrow [A] and filled lower black arrow [B]), which are prerequisites to performing BPV. BPV will reduce/abolish the gradient across the pulmonary valve, but the remaining subvalvar or supravalvular stenosis will prevent flooding of the lungs.[19,77,78] Reproduced from Rao *et al.*[78]

Long-term follow-up (defined as mean or median greater the 5 years) results of BPV have been investigated by several investigators.[68-75] These investigations reveal persistent effective relief of pulmonary valve obstruction along with the development of varying degrees of PI.[68-75]

3. Pulmonary stenosis associated with cyanotic congenital heart defects (CHDs)

Following the practice of using BPV for patients with isolated PS, as described in the preceding sections, the author and colleagues encountered an infant with d-transposition of the great vessels, a large ventricular septal defect (VSD), severe subvalvar and valvar PS, and hypoplastic pulmonary arteries. The data on this infant were presented to the surgeons who worked with the author with a recommendation for an aortopulmonary shunt. The surgerical colleagues hesitated to surgically intervene because the aortopulmonary shunt was likely to thrombose, given the diminished pulmonary arterial size. The following day, the infant was returned to the catheterization suite and underwent BPV. The procedure resulted in an increase in arterial oxygen saturation. Follow-up re-evaluation revealed good pulmonary arterial growth, and sometimes thereafter, the infant underwent successful surgical correction of the defect. Based on this experience, the author and colleagues applied this technique to other infants needing palliation of pulmonary oligemia. Rao[76] made a presentation demonstrating the utility of BPV in cyanotic heart disease patients at the Pediatric Cardiology International Congress Conference held in Vienna, Austria, in February of 1987. At the conclusion of the presentation, Dr. Michael Tynan, the chairman of the abstract session, congratulated the author and colleagues with thanks for introducing an additional indication for BPV. Thereafter, the author and colleagues, along with other cardiologists, used this technique to increase blood flow to the lungs as a substitute for a Blalock-Taussig shunt, effectively relieving pulmonary hypoperfusion and systemic arterial desaturation, as reviewed in the Rao,[19] Rao and Brais[77] publications. Rao,[19] Rao and Brais,[77] Rao *et al.*,[78] suggested balloon sizes slightly larger than pulmonary valve annulus diameter and require two or more obstructive elements in series (as demonstrated in Figures 42-44) to avoid flooding of the lungs.

Two cohorts of patients were studied by the author: the first consisted of eight infants,[76,77] and the second included fourteen patients.[78] The most common diagnoses were (i) Fallot's tetralogy and (ii) transposed great vessels with VSD and subvalvar and valvar PS. Peak pressure differences across the pulmonary valve were either eliminated or lowered after BPV, but the subvalvar gradient remained (Figure 45).[77,78] An increase in O2 saturation in the systemic circuit from 69.9 ± 11.5% to 81.4 ± 12.3 % ($P < 0.05$) (Figure 46), indexed blood flow to the lungs from 1.83 ± 0.55 to 3.15 ± 1.38 l/min/m^2 ($P < 0.05$) (Figure 47), pulmonary to

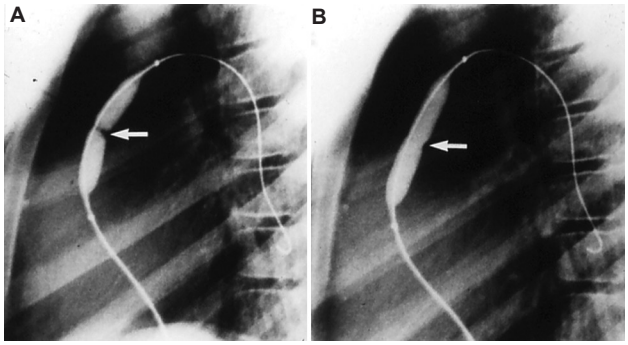

Figure 43. The balloon pulmonary valvuloplasty (BPV) procedure entails the insertion of a balloon valvuloplasty catheter through the stenotic pulmonary valve, followed by inflation with diluted contrast material. Balloon waisting is observed (A) as the balloon inflated (arrows). This waisting is caused by the narrowed pulmonary valve and disappears (arrow in [B]) with further balloon inflation, resulting in the relief of pulmonary valve obstruction. Only lateral views are displayed. Reproduced from Rao *et al.*[78]

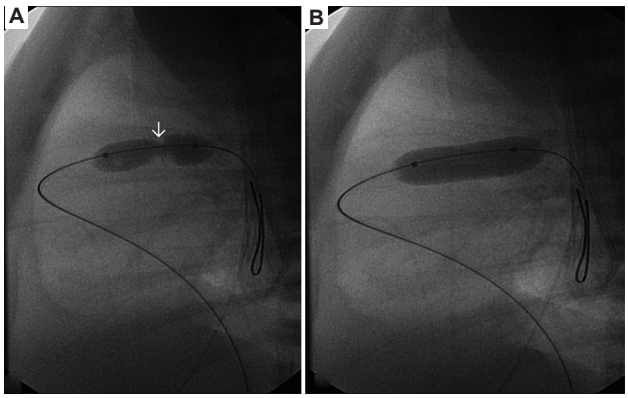

Figure 44. Similar to Figure 43, these cinefluorograms demonstrate the waisting of the balloon (arrow in [A]) during the early phase of inflation of the balloon. The waisting disappears (B) as the balloon is further inflated in another infant with a cyanotic congenital heart defect. Reproduced from Rao.[20]

systemic flow ratio (Qp: Qs) from 0.55 ± 0.36 to 1.19 ± 0.63 ($P < 0.05$) (Figure 47), and pulmonary artery pressures in systole from 15.5 ± 6.6 to 29.1 ± 12.1 mmHg ($P < 0.02$) occurred instantly after BPV. The patients underwent repeat cardiac catheterization six to 36 months later (13 ± 10 months); the data showed continued improvement in the aortic O2 saturation (82 ± 9%) (Figure 46), quantity of blood flow to the lungs (Figure 47), and Qp: Qs (Figure 47).[78] The most important feature of the results of BPV in these babies is the improvement of the pulmonary arterial diameter at follow-up, as illustrated in Figures 48 and 49. The results of BPV valvar PS in cyanotic CHD documented by other cardiologists[79-86] during the 5-year period (1987 – 1991) following the initial description of BPV for this group of patients are similar to what Rao,[76] Rao and Brais,[77] and Rao *et al.*[78] have observed.

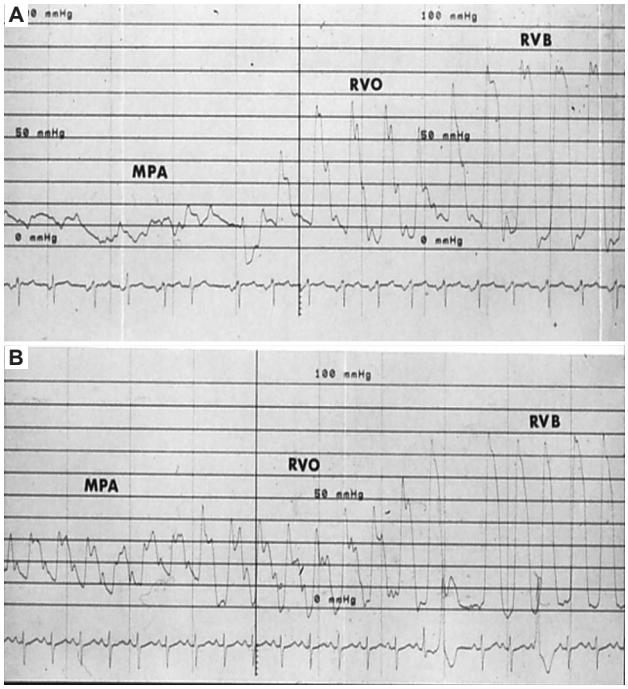

Figure 45. Valvar and subvalvar gradients before balloon pulmonary valvuloplasty (BPV) (A). After BPV, the pressure gradient across the pulmonary valve diminished while the subvalvar pressure gradient remained (B).
Abbreviations: MPA: Man pulmonary artery; RVB: Right ventricular body; RVO: Right ventricular outflow tract. Reproduced from Rao and Brais.[77]

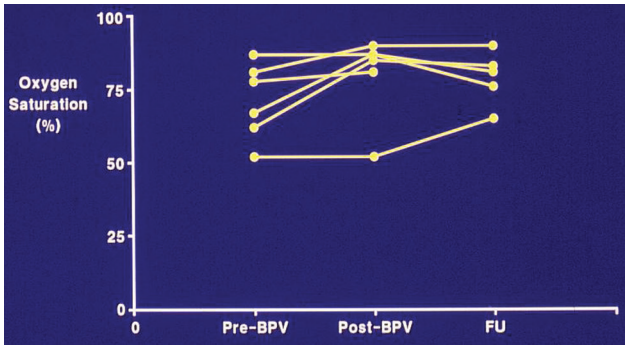

Figure 46. The improvement in arterial O2 saturation in the systemic circuit from pre-balloon pulmonary valvuloplasty (Pre-BPV) to that following BPV (post-BPV). At follow-up (FU), the improvement in O2 saturation persisted in most patients.

4. Obstructed pulmonary bioprosthetic valves

Both porcine heterografts and homografts have been used in the repair of certain cardiac defects, most notably variants of Fallot's tetralogy and common truncus. Over time, these valves tend to degenerate, leading to stenosis. A study has indicated that when the peak gradient across

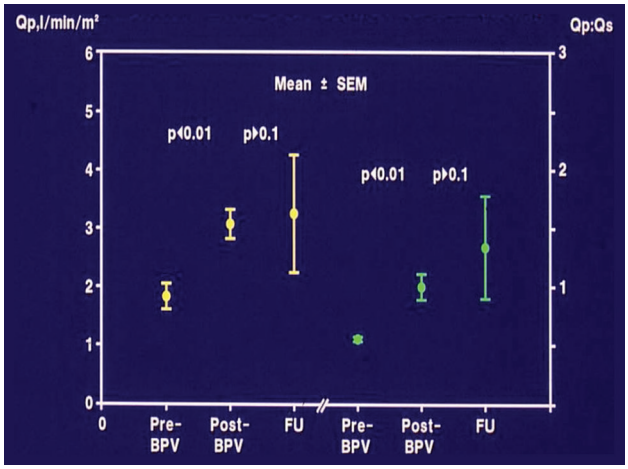

Figure 47. The outcome of balloon pulmonary valvuloplasty (BPV) on blood flow to the lungs (Qp) in l/min/m^2 (left group) and the ratio of blood flow between pulmonary and systemic circuits (Qp: Qs) (right group) both at the time of BPV and at follow-up (FU). A significant ($P < 0.01$) increase in Qp and Qp: Qs occurred after BPV. These measurements remained unaltered ($P > 0.1$) at FU. However, the standard errors of mean (SEM) are larger at FU. Replicated from Rao.[48]

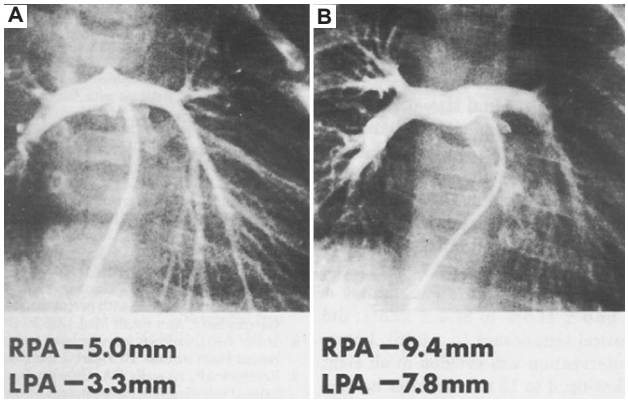

Figure 48. Cineangiographic images of pulmonary arteries immediately before (A) and 6 months following (B) balloon pulmonary valvuloplasty (BPV) in an infant with transposed great vessels, ventricular septal defect, and subvalvar and valvar pulmonary obstruction, illustrating improved diameters of the pulmonary arteries both on the right (RPA) and left (LPA) sides. There is a variation in magnification; both cineangiograms were performed with catheters of #5-F size. Following adjustment for magnification, the RPA improved from 5.0 mm to 9.4 mm and the LPA from 3.3 mm to 7.8 mm. Replicated from Rao and Brais.[77]

the pulmonary valve is higher than 50 mmHg, dilation of such valve becomes necessary.[19] The procedure of BPV mirrors that used for native PS (Figure 50). It is imperative that the balloon's diameter matches that of the initially implanted valve.[19,87] In the study, the patients had an average age of 14.9 ± 6.2 years at the time of BPV.[19] For the entire cohort, the peak systolic pressure difference through the porcine heterograft reduced from 77 ± 25 to 46 ± 29 mmHg, the peak systolic pressure in the right ventricle

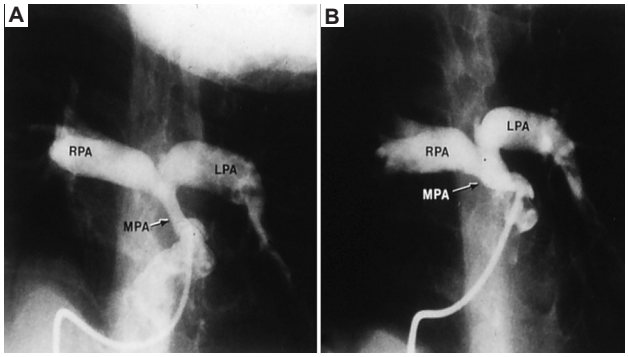

Figure 49. Cineangiographic images of the pulmonary artery immediately before (A) and 12 months after (B) balloon pulmonary valvuloplasty (BPV) in an infant with Fallot's tetralogy with subvalvar and valvar pulmonary obstruction, illustrating improved diameter of the main pulmonary artery (MPA) at follow-up. The left pulmonary artery (LPA) and right pulmonary artery (RPA) are labeled. Replicated from Rao *et al.*[78]

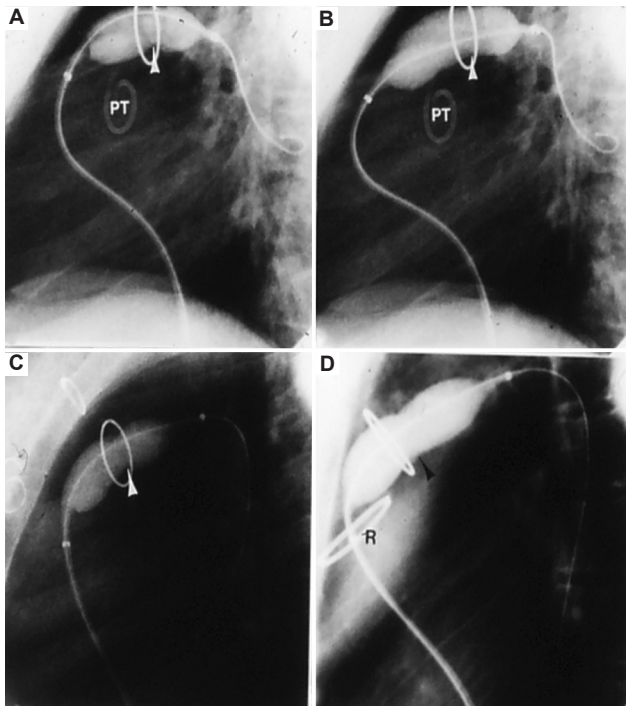

Figure 50. Balloon dilatation catheters positioned across the porcine heterografts (Hancock). The partially inflated balloon (A) shows the balloon "waisting" (arrowheads), almost entirely eliminated (B) with further balloon inflation. Fully inflated balloons are featured in two other patients (C and D). It is observed that waisting (arrows) persists to some extent in these two frames. In addition, note that the waisting (arrows) is just distal to the opaque metallic ring of the Hancock prosthesis. In (D), the connection between the right ventricle and conduit is marked by another ring (R). The pigtail (PT) catheter in the ascending aorta is labeled. Reproduced from Rao.[19]

decreased from 108 ± 33 to 88 ± 24 mmHg, and the right ventricle/left ventricle peak systolic pressure ratio declined from 0.94 ± 0.19 to 0.72 ± 0.22. While these results may

not be deemed excellent, the procedure did afford some relief of obstruction in some patients, contributing to a prolonged conduit life.[19,87] Rao[87] suggested that stents may be more useful in addressing this pathology.

5. Summary and conclusion

This paper presents a pictorial rendition of the author's observations regarding BPV for treating valvar PS, PS associated with cyanotic CHDs, and bioprosthetic valves in the pulmonary position. BPV results in a reduction of peak systolic pressure gradient across the pulmonary valve at the time of BPV and at both intermediate-term and long-term follow-ups. Difficulties such as RV infundibular stenosis, recurrence of stenosis at intermediate-term follow-up, and PI at long-term follow-up have been observed in isolated PS cases but occur infrequently. RV infundibular obstruction typically resolves in most patients, with some requiring beta-blocker therapy and rare instances that necessitate surgery. Successful repeat BPV has been performed to treat restenosis. To decrease the incidence and degree of PI, the author and colleagues have revised the suggestions for B/A ratios used in BPV from the previous 1.2 – 1.4 to 1.2 – 1.25. In cases with PS in association with cyanotic CHD, improvements in O2 saturations at the time of BPV and enhanced anatomy at follow-up have been observed. However, the BPV of bioprosthetic valves has resulted in only a minimal reduction of the gradient across the bioprosthetic valve, suggesting that stents may be a more effective option to tackle this issue.

Acknowledgments

A substantial number of echocardiographic pictures were used as figures in this paper, with a significant portion originating from examinations conducted at the Children's Memorial Hermann Hospital in Houston, Texas. I take this opportunity to thank the sonographers for their diligence in securing high-quality echocardiograms.

Funding

None.

Conflict of interest

The author declares no conflicts of interest.

Author contributions

This is a single-authored article.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

Further disclosures

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ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

Alzheimer's disease and Parkinson's disease dementia: Practical tips for physicians

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Abstract

Dementia is a progressive disorder that weakens the intellectual abilities and causes the cognitive, behavioral, and functional decline in occupational and social areas. This research is targeted to extract a profile for the dementia diagnostic and clinical characteristics by evaluating the near-term effects of Alzheimer's disease (AD) and Parkinson's disease dementia (PD-D). A total of 240 individuals, including 60 AD patients, 60 PD-D patients, and 120 healthy controls, were included in the study. Data of individuals treated in a local dementia outpatient clinic between 2013 and 2023 were obtained from the clinic database. AD and PD-D diagnoses were made based on the revised National Institute on Aging and Alzheimer's Association (NIA-AA) criteria and movement disorder society (MDS) clinical diagnostic criteria, respectively. Functional, clinical, and neuropsychological evaluations of the patients were made by the same neurologist. Dementia staging and daily living activities were determined and categorized. In the patient group, functionality and instrumental activities of daily living (ADLs) scores were significantly worse than those of the control group, but there was no difference between the AD and PD-D groups. Calculation, verbal fluency, word list, early learning, and clock drawing test scores were lower in the AD group than in the PD-D group. Apathy, disinhibition, elution, irritability, abnormal motor movements, sleep, and appetite scores were significantly higher in the patient group than in the control group. While depression parameters were not significantly different between all the groups, hallucinations and anxiety parameters were significantly higher in the PD-D group than in the AD group. As an important predictor of independent living and the burden of disease, functional impairment is an important issue in patients with AD compared to those with PD-D. This study also highlights the neuropsychiatric perception disorder in terms of functional loss in AD and significant anxiety disorder for PD-D accompanied by early functional losses.

Keywords: Functional loss; Alzheimer's disease; Parkinson's disease; Cognitive function; Dementia; Anxiety

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Citation: Karakılıc S, Oksuz N, Ghouri R, Ozdemir AA, Ozge A. Alzheimer's disease and Parkinson's disease dementia: Practical tips for physicians. *Brain & Heart*. 2024;2(1):1712. https://doi.org/10.36922/bh.1712

Received: August 29, 2023

Accepted: November 15, 2023

Published Online: November 28, 2023

1. Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are diseases with different pathophysiologic foundations. However, both diseases share many epidemiologic,

clinical, and pathogenic features. For instance, both are age-related disorders and are more common in individuals over the age of 65. At the cellular level in these diseases, neurodegenerative process occurs, leading to cell death, oxidative stress, excitotoxicity, senile plaques, nigral degeneration, and accumulation of cytoplasmic inclusions. Furthermore, they share overlapping clinical characteristics, such as extrapyramidal features and dementia[1].

AD, a progressive neurodegenerative disorder, poses one of the most formidable challenges to aging populations worldwide. It is the most common form of dementia and affects more than 25 million people worldwide. While it generally affects 5% of individuals over the age of 65, this rate rises to 25% in individuals over the age of 80[2]. It is characterized by a subtle yet insidious onset, often marked by initial symptoms that primarily affect memory and cognitive functions. These early signs, such as forgetfulness, difficulty in finding words, and impaired problem-solving, represent the tip of the iceberg caused by the complex pathological cascade unfolding within the brains of the patients. Neuropathologically, diffuse neuronal cell loss is accompanied by amyloid plaques and neurofibrillary tangles. AD is etiologically linked to the aggregation of amyloid-beta plaques and tau protein tangles, which leads to synaptic dysfunction and neuronal loss[3]. Loss of physical function will be added to these findings in the future. Definitive diagnosis of AD is only possible with postmortem neuropathological examination, but clinical diagnosis can be made with neuropsychological testing and exclusion of other forms of dementia[4]. Although imaging approaches are utilized in the process of making diagnosis, specific findings for the disease cannot be derived from the imaging studies at the onset of symptoms. Magnetic resonance imaging (MRI) findings in AD reveal a distinctive pattern of structural brain changes in disease progression. These imaging studies commonly depict cerebral atrophy, especially in regions crucial for memory and cognition, such as the hippocampus and the entorhinal cortex[5]. Moreover, white matter hyperintensities, which are non-specific to AD, are an indication of vascular damage often found in AD patients, further affecting their cognitive function[6]. Beyond regional atrophy, functional MRI (fMRI) studies have illuminated alterations in brain connectivity and network integrity, shedding light on the disruption of neural communication in AD[7]. The combination of structural and fMRI findings also advances our understanding of the complex neural changes underlying this devastating disorder. Understanding both the initial symptoms and underlying pathology of AD is crucial for early detection, accurate diagnosis, and management of this common and debilitating condition.

Parkinson's disease dementia (PD-D) is a significant and challenging aspect of PD, affecting a substantial portion of individuals with PD as the disease progresses. The prevalence of PD-D during the clinical course of PD varies between 28% and 44%. The time from the onset of early motor symptoms of PD, such as tremor and rigidity, to the onset of cognitive impairment in PD-D is associated with a complex and multifaceted mechanism[8]. PD-D typically starts with subtle changes in cognitive function, often manifesting as mild memory difficulties and difficulties in multitasking or problem-solving. These initial symptoms, however, foreshadow the intricate and debilitating cognitive decline that characterizes PD-D. The underlying pathology of PD-D shares commonalities with PD, involving the accumulation of abnormal protein aggregates, primarily alpha-synuclein, which leads to neurodegeneration in critical brain regions, including the substantia nigra and cortex[9,10]. The epidemiology of PD-D reveals intriguing insights, including the fact that the risk of developing dementia in PD increases with age, disease duration, and severity of motor symptoms[11]. In addition, gender differences may play a role, as some studies suggest that men with PD have a slightly higher risk of developing dementia compared with women[12]. In PD-D, MRI findings are also used to assist with diagnosis. In individuals with PD-D, MRI findings commonly reveal structural alterations within key brain regions involved in both motor and cognitive functions. Atrophy of the substantia nigra, a hallmark of PD, can be visualized using MRI, highlighting the neurodegenerative process that underlies the motor symptoms[13]. Importantly, MRI studies of PD-D also unveil significant changes in cortical and subcortical regions, including the frontal cortex and hippocampus, which are associated with cognitive impairment[14]. These MRI findings not only contribute to the understanding of the structural underpinnings of PD-D but also have clinical implications for early diagnosis and disease progression monitoring.

Despite the differences between PD-D and AD in terms of clinical, neuropathology, and neuroimaging findings, both pathological conditions share some similarities in different disease stages. While amnestic changes are more prominent in AD, more significant deterioration in executive functions is observed in PD-D[15]. We relied primarily on neuropsychological tests and neurological examinations to diagnose pathological conditions in the outpatient clinic. Unfortunately, more expensive tests such as fMRI or cerebrospinal fluid were not performed on every patient.

In this study, we aimed to create a profile for the diagnosis and clinical features of dementia by evaluating

the short-term effects of AD and PD-D. Together with this profile, our additional clinical perspective and practical advice will be useful to doctors working in polyclinics, where the volume of patients seen in outpatient departments is high and psychologists are not assigned. This study adds to our understanding of the interplay between initial symptoms and neuropathological processes in both types of dementia, highlighting the critical need for early diagnosis, timely intervention, and the development of targeted treatment strategies.

2. Materials and methods

Data of individuals treated at the Dementia Outpatient Clinic of Mersin University Faculty of Medicine Neurology Department between 2013 and 2023 were obtained from the clinic's electronic database (www.epikriz.com/dementiadataset), which contains the assessment results of all dementia patients treated at the clinic, as well as their demographic data, initial complaints, concomitant comorbidities, and all detailed neuropsychological test results, have been archived since 2007. To ensure patient confidentiality, only member neurologists can access this dataset. The data of these patients were evaluated and recorded by the same neurologists involved in this study. Since this study was retrospective, the neuropsychological tests previously recorded in our dataset and detailed below were used in this study. All neuropsychological tests were performed by means of face-to-face interviews with the patients and their relatives and recorded.

2.1. Study population and data collection

This study was approved by the local Ethics Committee of Mersin University (MEU.2013-304, October 10 2013). Patients who went to the dementia outpatient clinic of Mersin University Department of Neurology between 2013 and 2023 were enrolled in the study. Sixty patients diagnosed with AD, 60 patients diagnosed with PD-D, and 120 healthy controls were included in the study. Informed consent was obtained from all participants. The diagnosis of AD was made based on the revised NIA-AA criteria[16]. For the diagnosis of PD-D, Movement Disorder Society (MDS) clinical diagnostic criteria were used[17]. The control group was composed of spouses and first-degree relatives of the patients, who were living in the same geographical area and belonging to the same age range. No criteria were determined for selecting healthy control subjects based on gender and education level.

The exclusion criteria of this study are as follows: (i) Being under the age of 18, (ii) being pregnant, (iii) having a secondary medical cause that may affect cognitive performance, such as metabolic coma and psychiatric disorder, (iv) having other causes of dementia, (v) not able to converse in Turkish, and (vi) having auditory problems (hearing loss that cannot be corrected with a device). All participants were evaluated in the same clinic under the supervision of the senior physician (A.O.). The patients regularly visited the clinic every 3 months. Age, gender, formal education period, dominant hand, marital status, duration of the disease, thyroid dysfunction, vascular risk factors (diabetes mellitus, hypertension, hyperlipidemia, coronary and artery disease), alcohol consumption and smoking habit, and family history of dementia were evaluated. Neuropsychological assessments were carried out by a neurology resident and the results were entered into a web-based database. During each visit, the physician prescribed medications and ordered the patients for laboratory tests, if necessary. In addition, all patients underwent neurological examinations. All data were recorded in the electronic database (www.epikriz.com/dementiadataset) developed under the leadership of the Turkey Alzheimer's Study Group. The results of the neuropsychological tests listed below were retrieved from the database and used in this study:

(1) *Cognition*. Turkish-validated Mini-Mental State Examination (MMSE) was used in the screening test[18].

(2) *Numerical range*. The forward and backward digit-span test was used in our dataset. We used the following numerical sequences in our study: 28/51–372/494–5169/6294–83529/61074– 285164/917203–4072916/3508172[19].

(3) *Calculation*. In this study, we applied the following calculation problems: 5 + 3; 15 + 7; 31 – 8; 5 × 13; and 39/3. The maximum score for correctly answering all problems was 5[20].

(4) *Abstraction*. The participants were asked to interpret three different proverbs. Each correct answer was awarded with 1 point. The proverbs used in this test were "to be worn to the bone" (Tur. lit. "getting black water on my feet"), "he that lies down with dogs will rise up with fleas" (Tur. lit. "grapes grow darker by facing each other") and "as the twig is bent so is the tree inclined" (Tur. lit. "the tree is only bent when ripe"). These were chosen from among the most used Turkish proverbs[21].

(5) *The Word Memory Test* (*WMT*). This series of tests was used to assess verbal learning and memory through three learning experiments, delayed recall, and recognition subtests. In the learning experiments, the examiner verbally presented a set of 10 neutral nouns in different sequences, such as oil, building, arm, beach, letter, cat, stick, ticket, grass, and motor, with no adjectives to avoid bias. Patients were then asked to recall all the words they remember, and one point was awarded for each correct

word remembered. In the delayed recall stage, conducted after three additional tests, patients were asked to recall the words they previously learned. In the next step, a mixed list of 20 words, including 10 new words of similar nature, such as mosque, five, mountain, string, coffee, lira, slippers, soldier, hotel, and village, was presented to the patient, who was then asked to recognize the previously learned words. The total score for correct positive and false negative conditions in this stage is 20. During the administration of this test, a second pause was given before proceeding to the next task, and feedback about patient responses was not provided[22].

(6) *Boston Naming Test (BNT)*. It is a widely used neuropsychological test that assesses an individual's ability to name objects. The BNT consists of 60-line drawings of objects of increasing difficulty, and the participant was asked to name each object. One point was awarded for each correctly named object[23].

(7) *Clock Drawing Test (CDT)*. It is a widely used neuropsychological test that assesses an individual's ability to draw a clock face and set the hands to a specified time. The CDT is scored on a 10-point scale based on the accuracy of the drawing and the placement of the hands[24].

(8) *The Global Deterioration Scale (GDS)*. GDS for AD is a widely used tool for staging the progression of cognitive decline in individuals with AD. The GDS is based on a 7-point scale that ranges from no cognitive impairment to severe cognitive decline as follows:
- Grade 1: No cognitive impairment
- Grade 2: Questionable cognitive impairment
- Grade 3: Mild cognitive impairment
- Grade 4: Moderate cognitive impairment
- Grade 5: Moderately severe cognitive impairment
- Grade 6: Severe cognitive impairment
- Grade 7: Very severe cognitive impairment

The GDS is a widely used tool in clinical practice and research to measure the progression of AD. It provides a standardized way to assess the severity of cognitive decline and track changes over time[25].

(9) *Clinical Dementia Rating Scale (CDR)*. CDR is a global summary measure designed to identify the overall severity of dementia. Six different areas are assessed in this test, namely, memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. The CDR is based on a 5-point scale as follows:
- CDR-0: No cognitive impairment
- CDR-0.5: Questionable or very mild dementia
- CDR-1: Present, but mild dementia
- CDR-2: Moderate dementia
- CDR-3: Severe dementia
- CDR-4: Profound dementia
- CDR-5: Terminal dementia.

The overall CDR score was used to group patients according to the severity of dementia[26].

(10) *Blessed Dementia Rating Scale (BDRS)*. BDRS consists of 22 items and quantifies the degree of intellectual and personality deterioration in the elderly. BDRS reflects changes in daily performance, habits including self-care, and personality. The BDRS is scored on a 0–28 point scale, where higher points indicate a larger decrement in functional capacity[27].

For evaluating PD patients' daily living activities and disease staging, MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was used and all PD patients were evaluated during the period when Parkinson's patients are active in terms of motor movement ("ON period")[28].

2.2. Statistical analysis

STATISTICA 13.0 statistical program was used for statistical data entry and analysis. Number and percentage values were given as descriptive statistics for categorical variables and the Chi-square test was used in the analysis of categorical data. Mean, standard deviation, minimum, and maximum values were given as descriptive statistics for continuous variables satisfying the normal distribution condition. One-way analysis of variance (ANOVA) was used for the variables conforming to the normal distribution. Tukey's test was used to determine the significant difference between pairs of groups. Median, first quartile (Q1), and third quartile (Q3) values were used as descriptive statistics for continuous variables that did not meet the normal distribution condition and for these variables, Kruskall–Wallis test was used for data analysis. Results are given together with 95% confidence interval, and differences with $P < 0.05$ are considered significant.

3. Results

A total of 240 participants, including 115 men (47.9%), and 125 women (52.1%), with a mean age of 68.9 years, were analyzed in this study. There were differences between the AD and PD-D groups in terms of gender distribution, with the female proportion higher in the AD group while the male proportion was in the PD-D group ($P < 0.05$). There was also a difference in disease duration between the AD and PD-D patient groups, and the disease duration was longer in the PD-D group ($P < 0.05$). There were differences in age distribution between the patient groups and the control group ($P < 0.001$), but there was no difference in age distribution between the patient groups ($P > 0.05$). The demographic characteristics of patients are summarized in Table 1. Compared with the control group, the education period was shorter in AD and PD-D groups ($P = 0.001$).

Table 1. Demographic characteristics of the study participants

	AD (*n*=60)	PD-D (*n*=60)	Control (*n*=120)	*P*
Age, year (mean±SD)	71.4±6.11	73.32±7.07	65.49±7.00*	<0.001[a]
Gender (*n*, %)				0.031[b]
Female	37 (61.7)	23 (38.3)	65 (54.2)	
Male	23 (38.3)	37 (61.7)	55 (45.8)	
Disease duration, year (median, min-max)	3 (0 – 11)	4 (1 – 34)	-	<0.001[c]
Living (*n*, %)				
With family	41 (68.3)	41 (68.3)	97 (80.8)	0.080[b]
Alone	19 (31.7)	19 (31.7)	23 (19.2)	
Education period, year (median, min-max)	5 (0 – 16)	5 (0 – 17)	8 (0 – 22)*	0.001[d]
Dominant hand (*n*, %)				0.628[b]
Right-handed	53 (88.3)	49 (81.7)	104 (86.7)	
Left-handed	4 (6.7)	8 (13.3)	13 (10.8)	
No dominance	3 (5.0)	3 (5.0)	3 (2.5)	

Notes: [a]One-way ANOVA; [b]Chi-squared test; [c]Mann–Whitney U-test; [d]Kruskal–Wallis test; *compared with the control group.
Abbreviations: AD: Alzheimer's disease; PD-D: Parkinson's disease with dementia.

The presence of head injury, thyroid dysfunction, vascular risk factors, family history of dementia, smoking, and alcohol use were questioned and no statistically significant difference between the patient groups was found. The medical history and comorbidities of the patient groups are summarized in Table 2.

The BDRS functional test results revealed that there was a significant difference between the patient groups and the control group in changes in the performance of daily activities, personality, interests, and drive ($P < 0.001$), but there was no difference between the patient groups – AD and PD-D ($P > 0.05$). There was also a significant difference in the changes in habits scores, which were more pronounced in the PD-D group ($P < 0.05$; Table 3).

In terms of cognitive evaluation, a statistically significant difference was found between the patient groups and the control group in all relevant tests ($P < 0.001$; Table 4). In addition, there was statistical significance between the AD and PD-D groups in the domains of calculation, verbal fluency, WMT-step 1, and CDT. In the AD group, the scores were generally lower in these tests compared to the PD-D group, with marked deterioration in the above-mentioned aspects ($P < 0.05$; Table 4)

The evaluation of neuropsychiatric symptoms and psychopathologies in the study patients revealed a statistically significant difference between the patient group and the control group in terms of delirium, agitation, NPI total score, and NPI distress score ($P < 0.05$). However, apart from the worse delirium rates in the AD group ($P < 0.05$), there was no significant difference between AD and PD-D groups in terms of agitation, NPI total score, and NPI distress scores ($P > 0.05$; Table 5).

4. Discussion

Dementia presents a significant challenge to the health-care system, necessitating accurate diagnostic tools for distinguishing various forms of cognitive decline. This study delves into the comparative evaluation of functional impairment between AD and PD-D patients. The findings are instrumental for refining diagnostic profiles and providing clinical insights that are relevant for physicians dealing with high patient volume in outpatient settings.

In clinical practice, MMSE was applied to all patients complaining of forgetfulness. Clock drawing, verbal fluency, and calculation are the most commonly used assessments. These tests are known for their quick and easy evaluations. CDT is a widely used cognitive assessment tool that can yield valuable insights into the cognitive impairments seen in AD and PD-D. Most CDT results of AD patients show the characteristic pattern of deficits, often characterized by distorted clock faces, missing numbers, and incorrect time settings. These abnormalities in clock drawings reflect the impaired visuospatial and executive functions of AD patients, which are common features of the disease. In contrast, individuals with PD-D may also demonstrate CDT difficulties, albeit with a slightly different profile. PD-D patients tend to struggle with the fine motor aspects of the test, exemplified by irregular clock numbers and hands, which are indicative of their motor-related impairments[29,30]. Therefore, the specific nature of the deficits on CDT may differ among AD and PD-D patients, reflecting the distinctive cognitive and motor challenges associated with each condition.

Table 2. Clinical features of the study participants

	AD (*n*=60)	PD-D (*n*=60)	Total (*n*=120)	*P*[a]
Head injury (*n*, %)	18 (30.0)	17 (28.3)	35 (29.2)	0.841
Thyroid dysfunction (*n*, %)	7 (11.7)	13 (21.7)	20 (16.7)	0.142
Vascular risk factors (*n*, %)	48 (80.0)	44 (73.3)	92 (76.7)	0.388
Regular alcoholic (*n*, %)	6 (10.0)	10 (16.7)	16 (13.3)	0.283
Current smoker (*n*, %)	23 (38.3)	28 (46.7)	51 (42.5)	0.356
Family history of dementia (*n*, %)	21 (35.0)	21 (35.0)	42 (35.0)	1.00

Note: [a]Chi-squared test.
Abbreviations: AD: Alzheimer's disease; PD-D: Parkinson's disease with dementia

Table 3. Blessed Dementia Rating Scale scores of the study participants

	AD (*n*=60)		PD-D (*n*=60)		Control (*n*=120)		*P*[a]
	Median (min-max)	IQR	Median (min-max)	IQR	Median (min-max)	IQR	
Changes in the performance of daily activities	2.0 (1.0 – 8.0)	1.50 – 4.00	2.5 (1.0 – 9.0)	1.00 – 4.00	2.0* (1.0 – 8.0)	1.00 – 2.00	<0.001
Changes in habits	2.0 (1.0 – 19.0)	1.00 – 2.00	2.0 (1.0 – 14.0)	1.25 – 4.00	1.0 (1.0 – 3.0)	1.00 – 2.00	<0.001
Changes in personality, interests, and drive	17.0 (1.0 – 23.0)	12.00 – 21.00	17.5 (1.0 – 23.0)	12.25 – 20.75	22.0 (11.0 – 23.0)	21.00 – 23.00	<0.001

Notes: [a]Kruskal–Wallis test; *compared with the control group
Abbreviations: AD: Alzheimer's disease; IQR: Interquartile range; PD-D: Parkinson's disease with dementia.

Table 4. Cognitive evaluation of the study participants

	AD (*n*: 60)		PD-D (*n*: 60)		Control (*n*: 120)		*P*[a]
	Median (min-max)	IQR	Median (min-max)	IQR	Median (min-max)	IQR	
MMSE total	22.0 (7.0 – 30.0)	18.00 – 25.00	22.0 (8.0 – 29.0)	17.00 – 26.00	28.0 (20.0 – 30.0)	27.00 – 29.75	<0.001
Digit forward	4.0 (2.0 – 6.0)	4.00 – 5.00	4.0 (1.0 – 6.0)	3.00 – 4.25	5.0 (2.0 – 7.0)	4.00 – 5.00	<0.001
Digit backward	2.0 (1.0 – 4.0)	2.00 – 3.00	2.0 (1.0 – 6.0)	2.00 – 3.00	3.0 (2.0 – 6.0)	3.00 – 4.00	<0.001
Calculation	2.0 (1.0 – 5.0)	1.00 – 4.00	3.0 (1.0 – 5.0)	2.00 – 5.00	5.0 (1 – 6.0)	3.00 – 5.00	<0.001
Verbal fluency	11.0 (2.0 – 20.0)	7.25 – 13.75	14.0 (5.0 – 23.0)	10.00 – 16.00	17.0 (7.0-35.0)	14.00 – 20.00	<0.001
WMT- step 1	2.0 (1.0 – 5.0)	1.00 – 3.00	3.0 (1.0 – 6.0)	2.00 – 3.00	3.0 (1.0 – 8.0)	3.00 – 5.00	<0.001
WMT- step 2	3.0 (1.0 – 7.0)	2.00 – 4.00	4.0 (1.0 – 7.0)	2.00 – 4.00	5.5 (2.0 – 9.0)	4.00 – 7.00	<0.001
WMT- step 3	3.0 (1.0 – 7.0)	2.00 – 4.00	4.0 (1.0 – 7.0)	3.00 – 5.00	6.0 (2.0 – 9.0)	5.00 – 7.00	<0.001
BNT	9.0 (2.0 – 15.0)	7.00 – 12.75	9.0 (3.0 – 15.0)	8.00 – 11.00	13.0 (5.0 – 15.0)	11.00 – 14.75	<0.001
Comprehension	6.0 (1.0 – 6.0)	3.00 – 6.00	6.0 (1.0 – 6.0)	3.00 – 6.00	6.0 (3.0 – 6.0)	6.00 – 6.00	<0.001
Visual memory score	7.0 (1.0 – 11.0)	4.50 – 9.00	8.0 (2.0 – 11.0)	5.50 – 9.00	10.0 (2.0 – 11.0)	8.00 – 11.00	<0.001
WMT-recall	3.0 (1.0 – 7.0)	2.00 – 3.50	3.0 (1.0 – 5.0)	1.75 – 3.00	5.0 (1.0 – 9.0)	3.00 – 5.00	<0.001
WMT-recognition	13.0 (5.0 – 20.0)	10.00 – 16.00	16.0 (10.0 – 20.0)	14.00 – 17.25	19.0 (10.0 – 20.0)	17.00 – 20.00	<0.001
Visual memory recall	4.0 (1.0 – 11.0)	3.00 – 6.00	5.0 (1.0 – 11.0)	3.00 – 6.00	8.0 (1.0 – 11.0)	6.00 – 11.00	<0.001
CDT	6.0 (1.0 – 10.0)	3.00 – 8.00	7.0 (2.0 – 10.0)	5.00 – 10.00	10.0 (2.0 – 10.0)	9.00 – 10.00	<0.001

Note: [a]Kruskal–Wallis test.
Abbreviations: AD: Alzheimer's disease; BNT: Boston Naming Test; CDT: Clock drawing test; IQR: Interquartile range; MMSE: Mini-Mental State Examination; PD-D: Parkinson's disease with dementia; and WMT: Word memory test.

Verbal fluency tests are also valuable tools for assessing language and executive function in AD and PD-D patients. In AD, verbal fluency deficits typically manifest as reduced performance on both semantic and phonemic fluency

Table 5. Neuropsychiatric evaluation of the study participants

	AD (*n*=60)		PD-D (*n*=60)		Control (*n*=120)		*P*
	Median (min-max)	IQR	Median (min-max)	IQR	Median (min-max)	IQR	
Delirium	4 (2 – 8)	4.00 – 6.00	4 (2 – 8)	3.00 – 5.00	2 (2 – 4)	2.00 – 4.00	0.002
Hallucination	4 (1 – 9)	4.00 – 6.00	4 (2 – 8)	2.00 – 6.00	2 (2 – 2)	2.00 – 2.00	0.155
Agitation	4 (2 – 12)	4.00 – 6.00	4 (2 – 8)	2.00 – 6.00	4 (2 – 4)	2.00 – 4.00	0.026
Depression	5 (1 – 8)	4.00 – 6.00	4 (2 – 12)	2.00 – 4.00	4 (1 – 12)	4.00 – 6.00	0.198
Anxiety disorders	4 (2 – 9)	3.00 – 4.00	4 (2 – 8)	3.00 – 6.00	4 (1 – 6)	2.00 – 4.00	0.422
Apathy	4 (1 – 8)	2.50 – 4.50	4 (1 – 9)	2.25 – 4.75	4 (2 – 6)	2.50 – 5.50	0.957
Disinhibition	4 (2 – 9)	2.75 – 5.25	3 (2 – 8)	2.00 – 4.00	-	-	0.252
Irritability	4 (2 – 9)	3.00 – 5.00	3 (2 – 8)	1.50 – 5.50	-	-	0.963
Abnormal motor behavior	4 (3 – 12)	3.25 – 10.00	3 (1 – 8)	2.00 – 4.00	-	-	0.114
Sleep problem	4 (1 – 12)	2.00 – 4.00	4 (2 – 9)	2.00 – 6.00	4 (2 – 6)	4.00 – 4.00	0.730
Loss of appetite	4 (1 – 6)	1.75 – 4.25	2 (2 – 6)	2.00 – 4.00	2 (2 – 2)	2.00 – 2.00	0.682
NPI total score	12 (2 – 78)	8.00 – 20.00	16 (4 – 71)	12.00 – 27.00	7 (1 – 20)	4.00 – 10.00	<0.001
NPI distress score	8 (2 – 33)	5.00 – 13.50	11 (1 – 54)	8.00 – 15.00	4 (1 – 12)	2.00 – 6.00	<0.001

Note: [a]Kruskal – Wallis test.
Abbreviations: AD: Alzheimer's disease; IQR: Interquartile range; NPI: Neuropsychiatric inventory; PD-D: Parkinson's disease with dementia.

tasks. Individuals with AD often exhibit difficulties in generating words within specific categories (semantic fluency) and in producing words beginning with certain letters (phonemic fluency). These deficits are reflective of the widespread cortical atrophy and impairment of semantic memory systems seen in AD. In contrast, PD-D patients may display selective impairments in phonemic fluency while retaining relatively intact semantic fluency. This discrepancy likely relates to the differential patterns of brain involvement in PD-D, where executive dysfunction and motor symptoms play a prominent role. Thus, verbal fluency assessments can provide valuable insights into the distinct cognitive profiles of AD and PD-D, aiding in their differential diagnosis and management[31].

The assessment of calculation abilities in AD and PDD underscores the differing cognitive profiles of these two neurodegenerative disorders. Individuals with AD often exhibit marked impairments in numerical processing and calculation skills as the disease progresses[32]. These deficits may encompass impediments in basic arithmetic operations and higher-level mathematical tasks, reflecting the widespread cortical deterioration that affects multiple cognitive domains. In contrast, PD-D patients typically maintain their calculation abilities, even in the advanced stages of the disease[33]. This relative preservation of numerical skills in PD-D may be attributed to the distinct pattern of neurodegeneration in PD, which primarily affects subcortical regions while sparing the parietal and frontal cortices responsible for numerical processing. Consequently, the assessment of calculation abilities can serve as a useful diagnostic discriminator between AD and PD-D, highlighting the importance of a comprehensive neuropsychological evaluation.

4.1. Functional impairment in dementia

Functional impairment is a hallmark of dementia, with its impact extending beyond cognitive domains to daily activities, behavior, and quality of life. This study focuses on comparing the functional impairment between AD and PD-D, which is a critical indicator for distinguishing between different forms of dementia. Functional assessments, such as the BDRS, are used to evaluate performance in daily activities, personality changes, interests, and habits[27]. The recognition of these functional changes can provide clinicians with valuable diagnostic information and guide treatment strategies tailored to each patient's specific needs.

4.2. Importance of current diagnostic tools

The study showcases the utilization of well-established diagnostic criteria, including the revised NIA-AA criteria for AD diagnosis and the MDS clinical diagnostic criteria for PD-D diagnosis[16,17]. These criteria serve as essential tools that enable clinicians to accurately identify and differentiate between types of dementia, aiding in the selection of appropriate management strategies.

4.3. Physician's practical perspectives

The significance of this study lies in the considerations of the challenges faced by physicians who manage a high

volume of patients in outpatient clinics. With limited time and resources, clinicians require efficient diagnostic tools that can aid in accurate and rapid decision-making. Comprehensive assessments, encompassing MMSE, digit-span test, calculation, abstraction, and BNT, provide an overarching cognitive evaluation framework that can be efficiently integrated into the clinical workflow[18,19,20,23]. In this study, there was no statistical difference in the total MMSE scores, a clear indication that specific assessments, such as clock drawing, calculation, and verbal fluency, were required for a comprehensive evaluation.

4.4. Tailored approach to functional impairment

This study addresses the different patterns of cognitive decline among AD and PD-D patients. While both conditions share some common clinical features, such as memory impairment and cognitive dysfunction, differences in domains such as calculation and verbal fluency exist. These insights guide physicians in tailoring interventions to address the specific cognitive deficits associated with each condition[15,34].

4.5. Enhancing patient care in outpatient settings

This research has direct implications for enhancing patient care in busy outpatient settings. Physicians can leverage the presented diagnostic tools and criteria to streamline the diagnostic process and improve the accuracy of dementia diagnosis. By identifying functional impairments, cognitive deficits, and neuropsychiatric symptoms, clinicians can offer personalized care and interventions that cater to the unique needs of AD and PD-D patients.

The highlight of this study is the detailed examination of specific subsections within cognitive assessment tools, shedding light on the nuanced cognitive deficits that differentiate between AD and PD-D. The observation that scores of the MMSE show no statistical difference between the patient groups underscores the need for a more granular analysis of cognitive domains[35]. In this context, our study places emphasis on three key subsections: clock drawing, calculation, and verbal fluency.

4.5.1. Clock drawing

As a method of assessing visuospatial ability, clock drawing is a valuable approach for distinguishing between AD and PD-D. The ability to draw a clock face and set the hands to a specific time encapsulates intricate visuospatial and executive functions. Our findings align with previous research indicating that clock drawing performance is significantly worse in AD compared with PD-D. This discrepancy points to the selective impairment of visuospatial abilities in AD, a characteristic that can be leveraged in clinical assessments for differential diagnosis[24,36].

4.5.2. Calculation

Calculation skills are pivotal for evaluating cognitive flexibility and problem-solving abilities. The observed lower scores in calculation tasks within the AD group, compared with the PD-D group, accentuate the distinctive cognitive deficits in AD. The discrepancy hints at the potential role of calculation tasks as a discriminatory tool, showcasing the multifaceted nature of cognitive impairment across different types of dementia[20].

4.5.3. Verbal fluency

Verbal fluency tasks encompass a fusion of tests for probing language and executive functions, which reveal intricate aspects of cognitive decline. Verbal fluency, as assessed in this study, is an indicator of the disparities between AD and PD-D. Our findings corroborate the prevailing notion that AD primarily manifests as a language-based impairment, while PD-D often involves a more complex interplay of motor and cognitive deficits[15].

4.6. Limitations

Our study, while providing valuable insights into the differential functional and cognitive impairment profiles of AD and PD-D, is not devoid of limitations. The sample size may limit the generalizability of our findings, necessitating caution when extrapolating results to broader populations. In addition, the cross-sectional nature of the study limits our ability to establish causal relationships or trace the progression of functional and cognitive decline over time. Similar studies involving larger sample sizes will be able to provide more informative findings.

4.7. Implications

The meticulous examination of subsections within cognitive assessment tools carries implications that extend beyond diagnosis. Our findings underscore the necessity of incorporating detailed cognitive assessment in clinical practice, going beyond total scores to dissect cognitive domains. This approach helps enhance diagnostic accuracy, refine treatment planning, and customize interventions to cater to the cognitive deficits unique in different individuals. Moreover, subsections such as clock drawing, calculation, and verbal fluency are potential targeted cognitive assessment tools that lend themselves useful to clinicians in making differential diagnosis and planning personalized care.

5. Conclusion

Functional impairment is a linchpin in the differentiation of AD and PD-D, wielding immense implications for clinical practice. While the manifestation of cognitive

deficits is a common denominator in both neurologic conditions, the trajectories of functional deterioration of these conditions are distinctly demarcated. The utilization of tools like BDRS facilitates a deeper understanding of the nuanced behavioral and functional manifestations unique to each disorder. AD typically presents with a progressive decline in daily functioning, including ADLs and instrumental ADLs (IADLs), which involve widespread cortical involvement. Conversely, PD-D often has a relatively preserved functional capacity in the early stages, reflecting its etiological link to subcortical pathology, but later manifests motor and non-motor symptoms that significantly impact on independence. This differentiation in functional decline has profound implications for clinical decision-making, as it guides tailored interventions and care planning. By recognizing the divergent trajectories of functional decline, clinicians can refine diagnostic accuracy and formulate personalized treatment strategies. This approach, augmented by the promises of big data and patient-centered care, culminates in enhanced outcomes and improved quality of life for individuals grappling with the multifaceted challenges of dementia. In embracing this comprehensive approach, health-care providers can navigate the complex landscape of AD and PD-D more effectively, providing not only early diagnosis but also optimizing ongoing care and support to enhance the lives of those affected by these devastating conditions. In the future, new prospective studies involving larger patient cohorts should be conducted to further dissect their differences.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Ethics approval and consent to participate

This study was approved by the local Ethics Committee of Mersin University (MEU.2013-304, October 10 2013). Written informed consent form was obtained from all participants.

Consent for publication

There is no identifying information of the patients that appear in writing or within photograph.

Availability of data

The data used in this paper were obtained from a case-sensitive database that requires an institutional or physician-based subscription. Data used in this work are available from the corresponding author on reasonable request.

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ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

Sleep-induced limb vasodilation in individuals confined to bed for 24 h

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Abstract

The sleep/wake rhythm in limbs has been scarcely studied, especially due to the difficulty associated with continuous monitoring of arterial flow to the forearm and leg for a 24-h period. Addressing this constraint, we employed indium-gallium-in-silicone strain-gauge venous-occlusion plethysmography, an automated method facilitating the measurement of 24-h limb arterial flow in bed-confined subjects without disturbing their natural sleep. This article presents the state of the art in this field. Our examination of 60 healthy normotensive individuals revealed a distinctive sleep/wake rhythm in limb arterial flow, characterized by elevated values during sleep (32.7% in the forearm, $P < 0.0001$; 39.1% in the leg, $P < 0.0001$). Correspondingly, limb resistance mirrored the trend of flow (-32.7%, $P < 0.0001$; -33.5%, $P < 0.0001$), with these variations attributed to sleep-induced limb vasodilation. Sleep-associated vasodilation was also evident in 21 hypertensive individuals (leg resistance: -33.1%, $P < 0.0001$) and 13 heart transplant recipients lacking vagal and sympathetic cardiac innervation (resistance: -33.6%, $P < 0.0001$). On the contrary, among 11 subjects with an interrupted spinal cord, we observed forearm vasodilation (resistance: -36.6%, $P < 0.0001$) but observed no leg vasodilation if the spinal lesion was under T2 (innervating the leg). Furthermore, a loss of sleep-induced vasodilation occurred in both the forearm and leg if the injury was above C7 (innervating both forearm and leg). Our conclusion posits the existence of sleep-induced limb vasodilation, a phenomenon attributed to signals traveling along the spinal cord, with the heart playing no discernible role in this rhythmic process, and arterial hypertension deemed irrelevant. Comprehensive further studies are imperative to elucidate the precise triggers of limb vasodilation during sleep.

Keywords: Arterial flow; Peripheral resistance; Sleep-induced vasodilation; Strain-gauge plethysmography; 24-h continuous monitoring; Circadian; Spinal cord injury; Heart transplant

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Citation: Casiglia E, Tikhonoff V. Sleep-induced limb vasodilation in individuals confined to bed for 24 h. *Brain & Heart.* 2024;2(1):1886. https://doi.org/10.36922/bh.1886

Received: September 21, 2023

Accepted: December 11, 2023

Published Online: February 15, 2024

1. Introduction

The literature extensively documents circadian rhythms across various human organs and functions.[1-11] Notably, arterial blood pressure (BP) rhythms within limbs have undergone thorough investigation using both unrestricted intra-arterial[12-15] and indirect[16-20] monitoring methodologies. These studies consistently reveal a tendency for BP to be

higher during daytime compared to nighttime, probably influenced by mental and physical activity during waking hours.

While BP rhythms have received considerable attention, other aspects of limb hemodynamics, such as arterial flow and resistance, have been addressed to a lesser extent. This limited exploration is primarily attributed to the technical challenges associated with continuous 24-h monitoring of peripheral arterial flow – a prerequisite for resistance calculations.

Furthermore, to distinguish between circadian rhythms resulting from diurnal activity and those that are intrinsic (independent of activity), it is imperative to maintain subjects in a supine posture for 24 h. This protocol involves the stringent requirement of preventing any partial movements while in bed, effectively inhibiting involuntary movements during sleep – a task that proves challenging to realize.

2. Methods

Several years ago, our systematic exploration into the sleep/wake rhythm in limbs commenced, prompted by prior attempts in studies to monitor 24-h arterial flow in limbs. In animals, the attempt involved measuring the capillary diameter and erythrocyte speed,[21] while in humans, the approach utilized radioactive isotope clearance (^{14}Na, ^{133}Xe).[22-26] Unfortunately, these techniques solely measure skin and subcutaneous flow,[27] neglecting hemodynamically predominant muscular flow at rest. Although it was feasible to measure total limb arterial flow (skin + subcutaneous + muscular) by directly cannulating a large artery,[28] this method posed challenges for human application and encountered difficulties in obtaining approval from bioethic committees.

The optimal non-invasive method for continuous monitoring of total limb arterial flow is venous-occlusion plethysmography.[29] While water plethysmography offers precision, it proves impractical for 24-h recordings. Furthermore, drawing from previous studies, we found that air-,[30] impedance-,[31] and photo-plethysmography[32] are either imprecise or present difficulties in standardization.

Our pilot experiments have highlighted strain-gauge venous-occlusion plethysmography as the optimal method for conducting 24-h studies in subjects confined to bed. Our particular proficiency lies in the application of indium-gallium-in-silicone venous-occlusion strain-gauge plethysmography, a technique deeply ingrained in our experiments within the realm of human physiology.[33-41] This method, whose accuracy was unequivocally demonstrated,[42-45] employs a non-invasive approach using a plethysmographic fluximeter. Through a large-caliber tube connected to an under-pressure air reservoir, the technique incorporates periodic and automatic occlusion/deflation phases at over-venous-under-diastolic pressure (usually 50 mmHg).[42] This methodology facilitates the measurement of arterial flow in various body segments (for instance, legs and forearms) by analyzing the deflation slope coefficient according to automatic interpolation of the angle (α) of the initial deflation slope (Equation I), where x_i and y_i represent the experimental points, and n is their number.[34,35,38,42] Any measured values deviating from the norm are rectified by inner software.

$$\left\{\text{Coefficient} = \text{tg}\propto = \left[\begin{array}{l}\left(\sum_i \breve{}_i\right)\left(\sum_i {}^2_i\right) - \left(\sum_i {}_i\right)\left(\sum_i {}_i {}^2_i\right) \\ / \left[n_i y_i^2 - \left(\sum_i x_i\right)^2\right]\end{array}\right]\right\} \quad \text{(I)}$$

The presence of a professional observer throughout the 24-h study obviated the need for electroencephalographic ascertainment of sleep – a procedure that would have added complexity to the study procedure.

3. Results

3.1. Circadian rhythm in healthy volunteers

In a pilot experiment conducted on subjects confined to bed within a controlled environment – featuring a light blanket, a comfortable room with a stable temperature, and limbs immobilized by orthopedic devices – we demonstrated, for the first time, the existence of a circadian rhythm in limb arterial flow and resistance directly influenced by sleep, utilizing strain-gauge plethysmography.[46,47]

Sixty young and healthy volunteers underwent continuous recording of leg and forearm arterial flow while confined to bed for a 24-h period. Resistance was calculated in units of resistance (UR = mmHg × ml^{-1} × min × dl$_{tissue}$) derived from the mean BP to arterial flow ratio. Systolic and diastolic BP (in mmHg) were measured contemporaneously with every arterial flow detection using an automatic device, and mean BP was calculated from Equation II. All procedures were automated yet constantly controlled by an expert researcher. Importantly, the natural sleep of study subjects, visually monitored by researchers constantly present next to the examined subjects and responsible for measuring sleeping hours, remained undisturbed throughout the study.

$$\text{Mean} = (\text{systolic} + 2 \times \text{diastolic}) / 3 \quad \text{(II)}$$

With no *a priori* knowledge of the anticipated results, our observations in healthy subjects yielded a surprising revelation: arterial flow demonstrated a significant increase during sleep, both in the leg (39.1%, $P < 0.0001$)

and in the forearm (32.6%, $P < 0.0001$). Simultaneously, arterial resistance mirrored the trend of flow (−33.5%, $P < 0.001$ in the leg; −32.7%, $P < 0.001$ in the forearm).[46-50] Given the expected nocturnal decrease in BP and heart rate, and considering that subjects maintained a constant clinostatic posture while adhering to a standardized 24-h protocol, it became evident that elevated limb arterial flow could only be attributed to a sleep-induced arterial flow redistribution resulting from limb vasodilation. Figure 1 illustrates the 24-h leg flow of the very first subject as a representative example, with similar patterns observed in subsequent cases.[46-50] Crucially, in all cases, the variation in leg and forearm flow started earlier than the anticipated sleep-induced BP decline. This finding confirms that sleep-induced hemodynamic variations were the plausible cause, not the consequence, of the observed differences in the 24-h BP pattern.[8,47,48]

These fundamental pilot experiments, performed with the methodologies grounded in human physiology, indicated for the first time that the hemodynamic pattern in the limbs differed significantly during waking hours (lower flow and higher resistance) compared to sleep (higher flow and lower resistance). The confinement of subjects to bed in these experiments convinced us that this circadian rhythm in limb arterial flow and resistance was intrinsic and independent of daily activity. This finding not only fueled our commitment to the research program but also motivated our exploration into the underlying causes of what appeared to be a redistribution of blood to the limbs during sleep. Drawing inspiration from prior research demonstrating varying arterial flow and adrenergic drive in different organs throughout the day (although not specifically in relation to sleep), such as the kidney and liver,[10,11] we postulated that the variations in limb circulation represented a counter-regulatory mechanism – a form of blood reservoir essential for maintaining the characteristic "lower BP" associated with sleep.

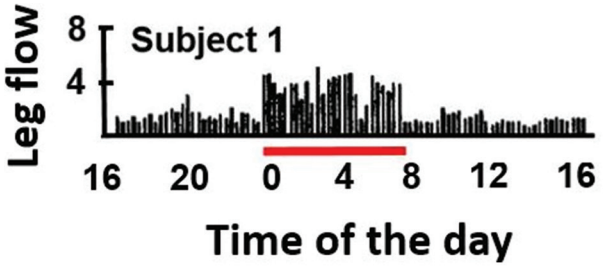

Figure 1. Plethysmographic monitoring of leg arterial flow (in mL × min^{-1}) in our very first case, a normotensive health volunteer man age 26 years confined to bed for 24 h constantly by an orthopedic device.[46] The other cases of our pilot studies in normal subjects had the same trend. The red line indicates the sleeping hours directly verified by a professional observer.

3.2. Circadian rhythm in hypertensive patients

As previously mentioned, our initial experiments were conducted on young, healthy, normotensive volunteers. Subsequently, the same circadian rhythm was identified in 35 untreated hypertensive patients with an average systolic BP of 142.2 ± 16.2/89.7 ± 9.1 mmHg. In these hypertensive subjects, forearm blood flow exhibited an increase (32.2%, $P < 0.0001$), while forearm resistance exhibited a decrease (-33%, $P < 0.0001$) during sleep compared to waking hours.[48,50] These observations were consistent across different age groups,[50] mirroring the trend previously observed in normotensive individuals.

3.3. Circadian rhythm in heart transplant recipients

We sought to investigate whether the circadian rhythm in limb arterial flow and resistance during sleep and waking hours is influenced by cardiac activity, which notably differs between the two states. To address this, we focused on heart transplant recipients, a group previously shown to lack a day/night (rather than wake/sleep) BP rhythm.[51,52] Our goal was to determine whether the circadian rhythm in limb arterial flow and resistance during sleep persists in heart transplant recipients, shedding light on whether the alternation between limb vasodilation and vasoconstriction during sleep is influenced by cardiac activity and its impact on arteriolar tone. The orthotopic heart transplant, performed according to the Shumway technique with atrial cuffs suture and termino-terminal anastomosis of the ascending aorta and pulmonary truncus before bifurcation, notoriously leads to the loss of vagally mediated as well as sympathetic-mediated heart control.[53,54] Consequently, the transplanted heart has no role in the autonomic control of peripheral hemodynamics. A previous spectral analysis performed the day before the 24-h bed study confirmed that heart-transplant recipients differed significantly from controls in this respect, exhibiting the expected lower heart rate variability for both low and high frequencies (Figure 2).[49]

In these subjects, leg arterial flow was found to be higher (26.6%, $P < 0.0001$), and leg resistance lower (-36.6%, $P < 0.0001$) during sleep compared to waking hours, mirroring the patterns observed in controls with native hearts. This outcome confirms that heart nerves do not contribute to sleep-dependent control of limb flow and resistance variations.[49]

3.4. Circadian rhythm in patients with spinal cord transection

The question of how sleep-induced variations in limb arterial flow and resistance occur remained to be clarified. Previous studies demonstrated that the day/night rhythm (distinct

from the wake/sleep rhythm, which had never been studied in bed-confined subjects before) was attenuated or nullified by lumbar sympathectomy or epidural anesthesia,[55-57] suggesting the involvement of signals transmitted through the spinal cord.

Conducting an experimental study to confirm this hypothesis through surgical interruption of the spinal cord was implausible in humans. However, a form of natural experiment already existed, involving subjects with traumatic medullary transection resulting in irreversible spinal cord interruption under T2 (clinically paraplegic) or above C7 (clinically tetraplegic). The former group was ideal for investigating the role of efferent nervous signals in the legs, while the latter was suitable for studying both forearms and legs.[58] These two patient groups were compared to each other and to able-bodied normotensive control subjects without any spinal lesions.[58]

The findings in our study revealed an expected circadian rhythm of peripheral hemodynamics in able-bodied controls, contrasting with subjects with transected spinal cords who lacked this phenomenon. This disparity underscores the reliance of the rhythm on top-down signals transmitted through the spinal cord, with variations corresponding to the topographic level of spinal injury. Specifically, the phenomenon manifested in the legs only if the lesion was under T2 and in both legs and forearms if it occurred at or above C7 (Table 1).

The question of whether the observed rhythm is attributable to sleep-induced vasodilatation or to vasoconstriction during waking hours remains unclear. We incline toward the hypothesis of limb vasodilation during sleep for several reasons. Other authors have observed a vasodilatory effect in legs after lumbar sympathectomy[55,56] and an increase in arterial flow in the dorsal pedis artery after high epidural anesthesia.[57] These conditions transiently mimic an interruption of spinal cord transmission. In addition, studies in physiology have demonstrated a decrease in sympathetic drive during sleep.[59,60] Furthermore, evidence from studies involving electrical stimulation of the spinal cord suggests that spinal fibers effectively transmit vasodilating signals.[61,62] Moreover, α-blockade abolishes any trend of forearm arterial flow and resistance in morning, afternoon, and evening in normal subjects (vasodilating stimuli transmitted through the spinal cord are α-adrenergic in nature). In contrast, nitroprusside (a non-adrenergic agonist) is ineffective in this respect.[63] Consequently, the most plausible deduction is that during sleep, limb arterial tone decreases in comparison to waking hours, even in subjects confined to bed, due to increased vasodilator nervous activity transmitted through the spinal cord. While the reasons behind this rhythm remain unknown, its mechanism is clearly neurovegetative. We withhold judgment, as no experiments specifically addressing this topic have been conducted, and none of the studies by other authors have analyzed the sleep/wake phases or been based on 24-h recordings.

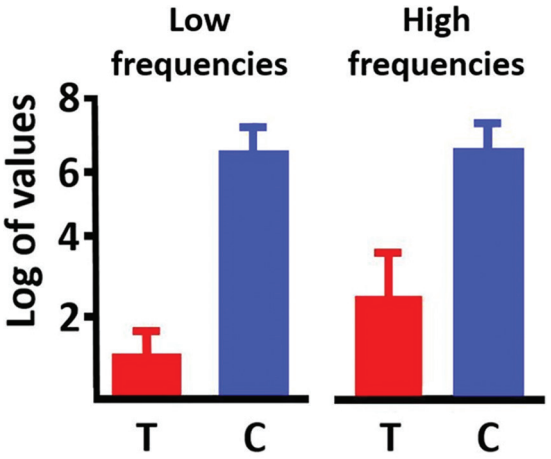

Figure 2. Spectral analysis of heart rate (RR intervals) for high and low frequency in the 13 heart transplanted subjects (T) and the 13 age-sex-matched controls (C) chosen for plethysmographic 14-h limb flow monitoring. The analysis was performed the day before limb flow monitoring.[49]

Table 1. Variations (in percentage) of limb arterial flow and resistance during sleep compared to waking hours in subjects with transected spinal cord under T2 (paraplegic) and above C7 (tetraplegic)

Parameters	Paraplegic (*n*=6)	Tetraplegic (*n*=5)
Forearm flow	36.5*	0
Forearm resistance	36.6*	0
Leg flow	0	−5.2
Leg resistance	−1.2	−1.0

Notes: The circadian rhythm of hemodynamics is preserved in the forearm but not in the leg in paraplegic patients, while it is lost both to the forearm and the leg in tetraplegic patients.[17,49] *P<0.0001 versus waking hours.

4. Discussion

We have demonstrated the existence of a circadian rhythm in arterial flow and resistance in both the leg and forearm of subjects confined to bed, independent of physical activity. Limb arterial flow exhibits higher values during sleep and lower values during waking hours. The observed patterns are mirrored by limb resistance. This vasodilation phenomenon may be responsible for the sensation of heat often experienced in the legs immediately before or during sleep. This circadian rhythm is associated with sleep/wake alternation, and it is consistently observed

in healthy normotensive subjects, hypertensive patients, and heart transplant recipients. Notably, heart transplant recipients lack a circadian day/night – not wake/sleep – hemodynamic alternation.[51,52] The mediation of this rhythm involves vasodilator stimuli traveling through the spinal cord in a top-down fashion, and its absence is noted when spinal fibers are interrupted. In patients with spinal cord injury, devoid of top-down nervous regulation, no limb vascular rhythm is observed. According to anatomical considerations, the leg circadian rhythm is absent in those with lesions under T2 (paraplegic), while both leg and forearm circadian rhythms are lost in those with lesions over C6 (tetraplegic).

Recent advancements, such as magnetic resonance imaging, have facilitated the measurement of limb flow (skin+subcutaneous+muscular) in humans.[64,65] However, this method is not suitable for continuous 24-h monitoring. Therefore, venous-occlusion strain-gauge plethysmography remains the optimal non-invasive method, and perhaps the only one, for monitoring sleep-induced variations in limb hemodynamics in subjects deliberately confined to bed.

5. Conclusion

The methodologies described here open new perspectives about the physiology of the peripheral arterial circle by revealing significant limb vasodilation during sleep, except in patients with spinal cord injury. The evidence that signals governing limb arterial flow and resistance rely on the integrity of the centripetal afferent nerve fibers answers one of the major questions in arterial circulation physiology and its compensatory mechanisms. From a clinical point of view, this finding underscores the need for special attention during the rehabilitation phase of paraplegic and tetraplegic individuals, as sleep-induced vasodilation mainly affects muscular mass. In a broader context, the sleep-induced limb vasodilation observed aligns with the concept that during sleep, especially in the lower limbs, sufficient freedom is needed to disperse body heat. Consequently, contrary to common practices in hospital rooms and private houses, maintaining a moderate bedroom temperature is advisable. The effects of thermal environments on sleep stages, tightly linked to thermoregulation, significantly affect the mechanisms regulating sleep. Notably, it is established that heat exposure increases wakefulness.[66]

Further studies on autonomic function, using other technological methods currently available or yet to be developed, are imperative to strengthen the findings presented herein. This is crucial for a more comprehensive understanding of this important aspect of cardiovascular physiology.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Edoardo Casiglia
Investigation: All authors
Methodology: All authors
Writing – original draft: All authors
Writing – review & editing: Edoardo Casiglia

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Data used in this work is available from the corresponding author upon reasonable request.

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ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

Efficacy and cognitive impact of modified Atkins diet in adults with drug-resistant epilepsy

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Abstract

This study aims to explore the efficacy and cognitive impact of the modified Atkins diet (MAD) in adults with drug-resistant epilepsy, as well as to analyze changes in epileptiform activity during ketogenic diet (KD) intervention. We performed a prospective, open-label study with patients aged 16 – 60 years who met the International League Against Epilepsy (ILAE) criteria for drug-resistant epilepsy. Sixteen patients were enrolled in this study, and baseline clinical and electroencephalography (EEG) characteristics, along with neuropsychological tests, were collected before and after 3 months of KD. Patients were divided into responders (≥50% seizure reduction) and non-responders (<50% seizure reduction) according to the clinical efficacy of the KD. Results indicate that 37.5% of patients reported a ≥50% seizure reduction after 3 months. In terms of safety, 37.5% of patients reported adverse effects, including constipation, abdominal pain, and nausea. In addition, a statistically significant increase in the level of total cholesterol was observed (P = 0.037) after diet treatment. Regarding cognitive impact, there was a significant improvement in auditory verbal learning test (AVLT) instant recall scale scores (P = 0.017). In terms of EEG characteristics, MAD significantly reduces interictal epileptic discharge (IED) index in non-rapid eye movement 2 (NREM2) after 3 months. No clinical predictors or EEG characteristics of MAD efficacy were identified. In conclusion, MAD can be safely and effectively practiced by adults with drug-resistant epilepsy. KD treatment has a significant impact on AVLT instant recall and can reduce the IED index in NREM2.

Keywords: Modified Atkins diet; Drug-resistant epilepsy; Cognitive function; Electroencephalography

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Citation: Liu H, Lu H, Ji Y, *et al*. Efficacy and cognitive impact of modified Atkins diet in adults with drug-resistant epilepsy. *Brain & Heart*. 2024;2(1):1978. https://doi.org/10.36922/bh.1978

Received: October 7, 2023

Accepted: January 5, 2024

Published Online: February 16, 2024

1. Introduction

Epilepsy affects almost 70 million people worldwide,[1] with nearly 10 million cases reported in China.[2] Despite treatments with antiseizure medications (ASMs), only two-thirds of patients achieve seizure freedom, leaving one-third classified as refractory to ASMs. The 2010 International League Against Epilepsy defines drug-resistant epilepsy as the lack of sustained seizure freedom despite the use of two tolerated, appropriately chosen and used ASMs.[3] Current treatment options for refractory epilepsy include surgery, neurostimulation, ketogenic diet (KD), and other new treatment prospects.[4]

In 1921, Dr. Wilder introduced the KD—a low-carbohydrate, high-fat diet—for epilepsy treatment.[5] However, the discovery and development of antiseizure drugs postponed further exploration of the KD after 1938. It was not until 1994 that the KD experienced a resurgence in clinical epilepsy studies.

The classical KD (CKD) was first used for children with refractory epilepsy, involving a one- or two-day fast in the hospital before initiating CKD to induce rapid ketosis. However, CKD poses challenges due to its high fat and severely restricted calorie, protein, and fluid requirements, resulting in low retention and tolerability. To address these limitations, a less restrictive KD known as the modified Atkins diet (MAD) was developed for use in adults with refractory epilepsy. In contrast to CKD, MAD treatment is initiated on an outpatient basis without a fasting period and lacks calorie restrictions. Over the past two decades, KD treatment has been widely applied to children with drug-resistant epilepsy, with established efficacy and safety.[6-8] However, the efficacy of MAD in adults with drug-resistant epilepsy remains elucidated only in several epilepsy centers.[9,10] In addition, the impact of MAD on epileptiform discharge remains unclear.

Recent findings indicate that the KD not only reduces seizure frequency but also improves behavioral and cognitive functions in children with refractory epilepsy, which include vocabulary, adaptation, and gross motor skills.[11,12] However, previous studies assessing cognitive improvements in adults with refractory epilepsy relied solely on subjective evaluations from patients and their families.[13] Objective cognitive scales were seldom employed to investigate the impact of the KD on cognitive function.

Our study aims to explore the efficacy, safety, and cognitive impact of MAD in adults with drug-resistant epilepsy. Furthermore, we seek to analyze changes in epileptiform activity during MAD.

2. Methods

2.1. Patients

Sixteen patients diagnosed with drug-resistant epilepsy at Xuanwu Hospital between May 2021 and January 2023 were enrolled in our study. The inclusion criteria were as follows: (i) Age 16 – 60; (ii) experiencing at least three countable seizures per month; (iii) ensuring that the doses of ASMs remained unchanged; (iv) having a body mass index >18.5 kg/m^2. Exclusion criteria were as follows: (i) Previous use of KD treatment; (ii) undergoing surgery or neurostimulation in the previous 12 months; (iii) pregnancy or planning for pregnancy; (iv) severe intellectual impairments; (v) possessing other contraindications to the KD; and (vi) unavailable for follow-up.

2.2. Study design and data collection

We conducted a single-center, prospective, and open-label study with a 3-month follow-up period. Clinical information, neuropsychological scales, and 2-h electroencephalography (EEG) were collected before initiation and after 3 months of KD treatment. The MAD treatment with medium-chain triglyceride added was conducted in this study. The effect of MAD on seizure frequency was assessed by Engel classification. Patients were considered responders if they had ≥50% seizure reduction and non-responders if they had <50% seizure reduction from baseline. Written informed consent was obtained from all the participants or their guardians.

The sentence should be revised to During the MAD treatment, a ketogenic dietitian and a doctor guided the diet treatment together. The estimated energy requirements of patients were calculated according to their baseline data. All patients received a document from the dietitian, including instructions on how to follow the diet and acceptable recipes. MAD was prescribed to provide a minimum of 65% of total calories from fat.[14] Carbohydrates were limited to 15 – 30 g/day[14] (approximately 5% of total calories). Urine ketones were monitored to assess the level of ketosis and compliance.[15] Patients were followed up through telephone calls at 2 weeks, 4 weeks, and 2 months after starting the diet. A clinical appointment was arranged 3 months after initiation to reevaluate laboratory tests, neuropsychological scales, and EEG.

Data obtained at baseline included demographic information, detailed seizure characteristics, and previous history. We collected information on the age of seizure onset, seizure types, duration of seizures, seizure frequency, and the number of ASMs. Previous history encompassed surgical history and a history of febrile convulsions. Baseline seizure frequency was assessed according to the average of 3 months before initiation.

To evaluate the safety of MAD, we also recorded the blood tests. Blood tests mainly focused on lipid metabolism (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total triglycerides), glucose metabolism (fasting blood glucose), and liver and kidney metabolism biomarkers (aspartate aminotransferase, alanine aminotransferase, creatinine, blood urea nitrogen).

Neuropsychological scale assessments, including the auditory verbal learning test (AVLT) instant recall, choice reaction time, and visual searching task, were performed to evaluate the memory, alertness, and attention functions of patients. These tests were conducted using a web-based system called the "Online Psychological Experiment System" (47.95.214.92/lattice/).

EEG was recorded according to the international 10 – 20 system at a sampling rate of 1024 Hz (580-G2CGSS, Biologic Co., USA). Epileptiform abnormalities were assessed using both longitudinal bipolar montage and average montage. A 2-h or long EEG session, covering wakefulness and light sleep periods, was performed for all patients. We measured the discharge pattern, distribution of discharge, presence of background rhythm slowing, focal slow wave, presence of prolonged discharges, generalized polyspike train (GPT), and generalized paroxysmal fast activity (GPFA). According to Sun *et al.*, GPT was defined as a high-amplitude burst of at least five generalized rhythmic discharges with frontal predominance, lasting less than 1 s.[16] GPFA was defined as a generalized activity in the beta frequency lasting at least 1 s and standing out from background rhythms.[17]

We randomly selected 10 min of EEG during wakefulness and 5 min during light sleep without artifact to analyze the interictal epileptic discharge (IED) index:

The seconds containing discharges/The total seconds*100% (I)

2.3. Statistics analysis

Patient characteristics were summarized, and comparisons were made using appropriate descriptive statistics. Variables were assessed for normal distribution, and quantitative data were presented as mean or median values. For normally distributed variables among groups before and after MAD treatment, the paired *t*-test was employed, while non-normally distributed variables were analyzed with the paired Wilcoxon signed-rank test. Among the groups of responders and non-responders, normally distributed variables were compared with the independent *t*-test, and non-normally distributed variables were tested with the nonparametric Mann–Whitney test. Categorical data were summarized using frequencies and percentages, and comparisons were made using the Chi-square test or Fisher's exact test. For neurophysiological tests, test-retest reliability was initially analyzed. Changes in neuropsychological scales scores were calculated as follows:

After diet values−Baseline values/Baseline values*100% (II)

Since higher scores represented different meanings in different neurophysiological scales, we standardized the positive value to indicate improvement in cognitive function scales. The change in the IED index was calculated as:

IEDs after 3 months−Baseline IEDs/Baseline IEDs)*100% (III)

Where a negative value indicates a reduction in the IED index. Statistical significance was set at $P < 0.05$; all statistical analyses were conducted using SPSS 25.0 (IBM Co., USA).

3. Results

3.1. Clinical characteristics and demographic information

Out of the 52 initially recruited patients, only 16 patients were eventually enrolled in our study, with 12 of them being male. The average age at follow-up was 20.00 ± 4.03 years, and the mean age of onset was 8.06 ± 5.21 years. However, only eight of them successfully completed the 3-month diet treatment. The flowchart in Figure 1 outlines the reasons for patients' withdrawal and exclusion from the study. Among the patients who completed the KD treatment, the mean age of onset was 11.50 ± 4.50 years, the mean age of commencing MAD was 21.12 ± 4.49 years, the mean duration of epilepsy was 9.63 ± 5.55, the average years of schooling was 9.38 ± 3.96 years, the mean number of previous ASMs was 3.13 ± 1.64, the mean number of current ASMs was 3.13 ± 1.00, the mean number of total ASMs tried was 6.25 ± 1.49, the mean weight loss was 3.19 ± 1.85 kg. Table 1 provides a detailed overview of the baseline characteristics of enrolled patients and a predictive analysis of MAD efficacy. In addition, a comparison between data

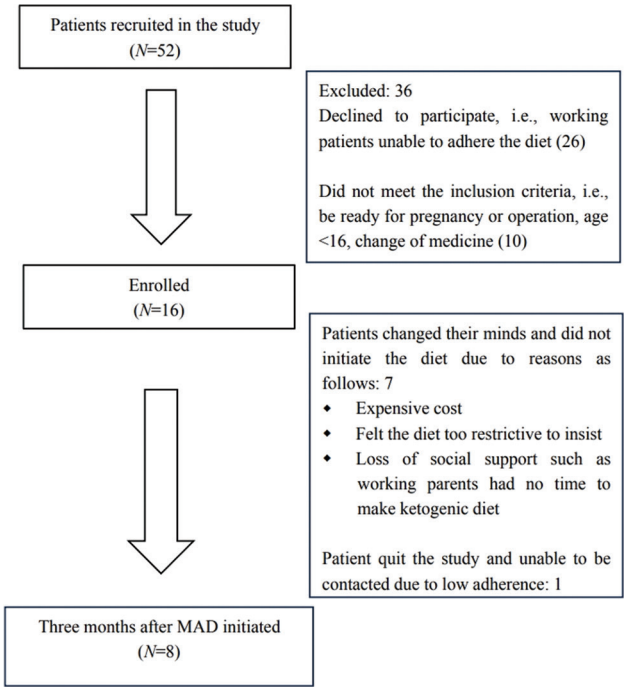

Figure 1. Flowchart of the study, depicting the number of patients recruited, patients enrolled, and patients as-treated (insisted 3 months after initiating the modified Atkins diet).

Table 1. Baseline characteristics and predictive analysis of modified Atkins diet efficacy

	Patients enrolled (*N*=16)	Patients who dropped out (*N*=8)	Patients as-treated (*N*=8)		*P*-value	*P*-value*
			Responders (*N*=3)	Non-responders (*N*=5)		
Gender (male %)	12 (75%)	4 (50%)	3 (100%)	5 (100%)		0.070
Age (year)	20.00±4.03	18.88±3.44	25.00±4.36	18.80±2.76	0.051	0.234
Age of onset (year)	8.06±5.21	4.63±3.30	13.67±4.93	10.20±4.21	0.328	0.235
Duration (year)	11.94±6.10	14.25±6.07	11.33±3.79	8.60±6.58	0.543	0.816
Years of schooling (year)	9.62±3.26	9.88±2.64	10.33±5.13	8.80±3.63	0.634	0.290
Occupation						
At home	9 (56.25%)	4 (50%)	2 (66.67%)	3 (60%)		
Student/work	7 (43.75%)	4 (50%)	1 (33.33%)	2 (40%)	1.000	1.000
Epilepsy type						
Focal	13 (81.25%)	6 (75%)	3 (100%)	4 (80%)		
Generalized	3 (18.75%)	2 (25%)	0	1 (20%)	1.000	1.000
Seizure frequency (month)						
<20	8 (50%)	4 (50%)	2 (66.67%)	2 (40%)		
20 – 40	3 (18.75%)	1 (12.50%)	1 (33.33%)	1 (20%)		
>40	5 (31.25%)	3 (37.50%)	0	2 (40%)	0.714	1.000
Number of previous ASMs	2.94±1.65	2.75±1.75	2.00±1.00	3.80±1.64	0.142	0.721
Number of current ASMs	3.00±0.89	2.88±0.84	3.33±0.58	3.00±1.23	0.680	0.721
Number of total ASMs tried	5.94±1.97	5.63±1.69	5.33±0.58	6.80±1.64	0.383	0.857
Febrile convulsive	2 (12.50%)	1 (12.50%)	1 (33.33%)	0	0.375	1.000
Surgical operation	4 (25%)	1 (12.50%)	1 (33.33%)	2 (40%)	0.714	0.569
Abnormal MRI	10 (62.50%)	5 (62.50%)	3 (100%)	2 (40%)	0.179	0.608

Notes: Continuous variables are presented as mean±SD, and categorical variables are presented as percentages. *P* value was calculated using Fisher's exact test for categorical data and independent t-test, or nonparametric Mann–Whitney test for continuous data; $P<0.05$ were considered to be significant. **P*-value was calculated between patients as-treated and those who dropped out.
Abbreviations: ASMs: Antiseizure medications; MRI: Magnetic resonance imaging; SD: Standard deviation.

from patients who adhered to the treatment and those who dropped out is presented.

3.2. Efficacy, retention, and safety of the MAD

3.2.1. Efficacy of the MAD

Among the eight patients who completed the study, three patients (37.5%) demonstrated a seizure reduction of ≥50%, three patients (37.5%) reported a seizure reduction of 25 – 50%, while one patient (12.5%) experienced no change, and one patient (12.5%) exhibited worsening of seizures. The total efficacy rate was 37.5%.

3.2.2. Retention of the MAD

Out of the 16 patients, seven did not initiate the diet treatment, and one patient failed to complete it due to low compliance. The reasons for dropouts are illustrated in Figure 1. The retention rates were 50% (8/16) at 3 months, 12.5% (2/16) at 6 months, and 6.25% (1/16) at 12 months.

3.2.3. The safety of the MAD

Among the eight patients, three experienced adverse effects. The first had diarrhea, the second had abdominal pain, and the third had nausea, resulting in a total adverse effect rate of 37.5%. However, these symptoms were mild and could be corrected with minimal interventions. In addition, we further explored the effect of MAD treatment on blood metabolism indicators and found that the treatment increased the level of serum total cholesterol (Table 2). No significant differences were observed between KD treatment and total triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, alanine aminotransferase, aspartate aminotransferase, urea nitrogen, and creatinine.

3.3. Analysis of the impact of MAD on cognitive function

3.3.1. Impact of MAD on cognitive function

Test-retest reliability was initially analyzed for neuropsychological tests ($P = 0.022$), indicating high retest

reliability. A statistically significant difference in the AVLT instant recall test ($P < 0.05$) was observed between the two groups. However, no significant differences were found between the groups in choice reaction time and visual searching task (Figure 2).

3.3.2. Comparison of the change in neuropsychological scale scores based on different MAD treatment efficacies

The change in neuropsychological scales is defined using Equation II. However, no significant difference was identified between the clinical efficacy of the KD and the change in neuropsychological scales (Figure 3).

3.4. Analysis of the impact of MAD on EEG

3.4.1. Relationship between EEG discharge pattern and clinical efficacy of MAD

Among the eight patients, seven exhibited focal discharge, and one patient demonstrated generalized discharge. In addition, three patients showed slowing of posterior dominant rhythm, four patients displayed focal slow waves, three patients presented GPT, and two patients had GPFA. The detailed EEG discharge pattern is presented in Table 3. We conducted an analysis to explore the correlation between the clinical efficacy of MAD and EEG discharge patterns. However, no significant predictive factors were identified (Table 3).

3.4.2. Impact of MAD on IEDs index

The IED index during wakefulness, non-rapid eye movement 1 (NREM1) and NREM2 stages of light sleep was analyzed to investigate whether MAD treatment can reduce epileptiform discharges. The results indicated that MAD treatment significantly decreased the IED index in NREM2 after 3 months (Figure 4). Subsequently, we explored the comparison of the baseline IED index between different MAD treatment efficacies. We further calculated the change in the IED index, defined using Equation III. However, the result showed no significant difference (Figure 5).

4. Discussion

In this prospective, open-label study, we explored the efficacy, retention, and safety of MAD treatment in adults

Table 2. Effects of modified Atkins diet on blood tests in patients who completed the study (*N*=8)

Marker (unit)	Baseline	3 months after KD	*d*-value	*P*-value*
Total triglycerides (mmol/L)	1.51±0.43	1.31±0.75	−0.20±0.43	0.226
Total cholesterol (mmol/L)	4.90±1.16	5.27±1.22	0.37±0.41	0.037
LDL (mmol/L)	3.11±1.11	3.33±1.24	0.23±0.42	0.166
HDL (mmol/L)	1.27±0.25	1.29±0.18	0.01±0.14	0.786
ALT (IU/L)	30±13	22±13	−7±11	0.102
AST (IU/L)	24±10	20±8	−4±9	0.282
FBG (mmol/L)	4.73±0.32	4.92±0.49	0.19±0.44	0.256
Urea nitrogen (mmol/L)	4.86±1.17	5.54±2.20	0.69±1.39	0.205
Creatinine (μmol/L)	63±10	65±13	2±6	0.490

Notes: Continuous variables are presented as mean±SD. *P-value was calculated using paired t-test for continuous data.
Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FBG: Fast blood glucose; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; KD: Ketonic diet.

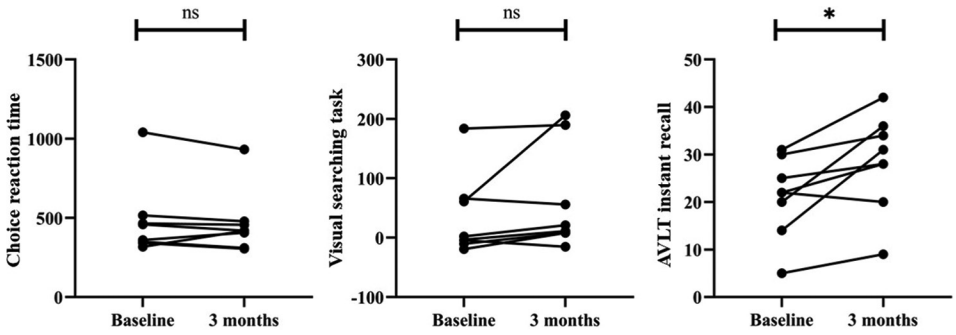

Figure 2. Impact of modified Atkins diet (MAD) on cognitive function in patients as-treated. Paired t-test was used to compare the neuropsychological scale scores before and after MAD treatment. *P<0.05; ns: Not significant.
Abbreviation: AVLT: auditory verbal learning test.

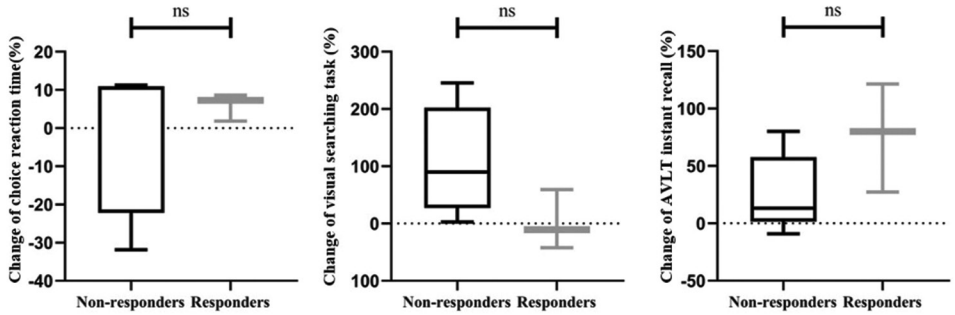

Figure 3. The comparison of the change of neuropsychological scale scores between responders and non-responders to modified Atkins diet treatment. An independent *t*-test was performed to compare the change in neuropsychological scale scores between non-responders and responders.
Abbreviation: AVLT: Auditory verbal learning test.

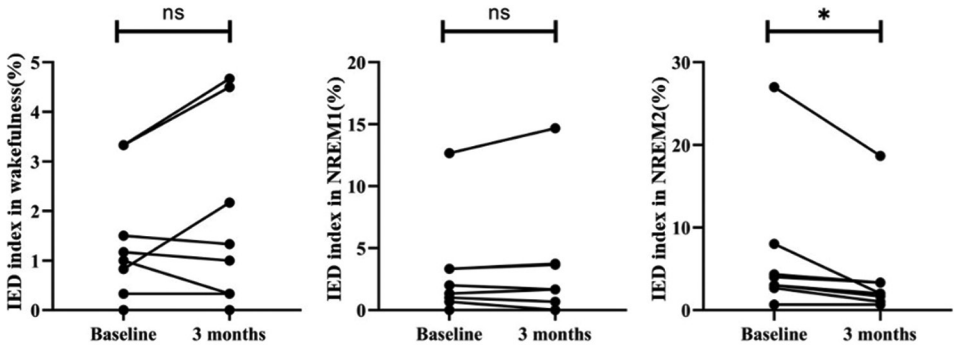

Figure 4. The impact of modified Atkins diet treatment (MAD) on interictal epileptic discharge (IED) index in patients as-treated. A paired *t*-test or paired Wilcoxon signed-rank test was used to analyze the difference in the IED index before and after MAD treatment. **P*<0.05; ns: not significant.
Abbreviations: NREM1: Non-rapid eye movement 1; NREM2: Non-rapid eye movement 2.

Table 3. Correlation between electroencephalography characteristics and clinical efficacy of modified Atkins diet in patients as-treated (*N*=8)

	Responders (*N*=3)	Non-responders (*N*=5)	*P*-value*
Discharge pattern			0.625
Focal discharge	3 (100%)	4 (80%)	
Generalized discharge	0 (0%)	1 (20%)	
Distribution of ED			0.643
Frontal region	0 (0%)	2 (40%)	
Central region	0 (0%)	1 (20%)	
Temporal region	3 (100%)	2 (40%)	
Slowing of the PDR	1 (33%)	2 (40%)	0.714
Focal slow wave	1 (33%)	3 (60%)	0.500
GPT	0 (0%)	3 (60%)	0.196
GPFA	0 (0%)	2 (40%)	0.464
Prolonged ED	1 (33%)	3 (60%)	0.500

Notes: Categorical variables are presented as percentages. **P*-value was calculated using Fisher's exact test for categorical data.
Abbreviations: ED: Epileptic discharges; GPFA: Generalized paroxysmal fast activity; GPT: Generalized polyspike train; PDR: Posterior dominant rhythm.

with drug-resistant epilepsy. We analyzed the impact of cognitive function using objective neuropsychological scales and investigated EEG characteristics and the IED index to identify predictive factors.

A considerable body of data has accumulated regarding the efficacy of KD in both children and adults. A meta-analysis of 12 studies reported a combined efficacy rate of 42% for CKD in adults with intractable epilepsy, and the efficacy rate of MAD is 34%.[18] Another meta-analysis of six randomized controlled trials indicated that MAD, when combined with standard ASM therapy, was associated with a higher rate of 50% or greater seizure reduction in frequency than standard ASM therapy alone.[19] Consistent with other studies,[20,21] the efficacy observed in our study was 37.5%. However, 62.5% of patients as-treated did not benefit from MAD treatment, and one patient even experienced worsening seizures. A meta-analysis of 16 observational studies revealed a seizure reduction rate below 50%, ranging from 12% to 67%,[22] and the proportion of seizure worsening was not specified. The mechanisms underlying seizure deterioration remain unclear. Previous studies suggested several potential causes: (i) The resistance to KD, where KD may change EEG patterns by

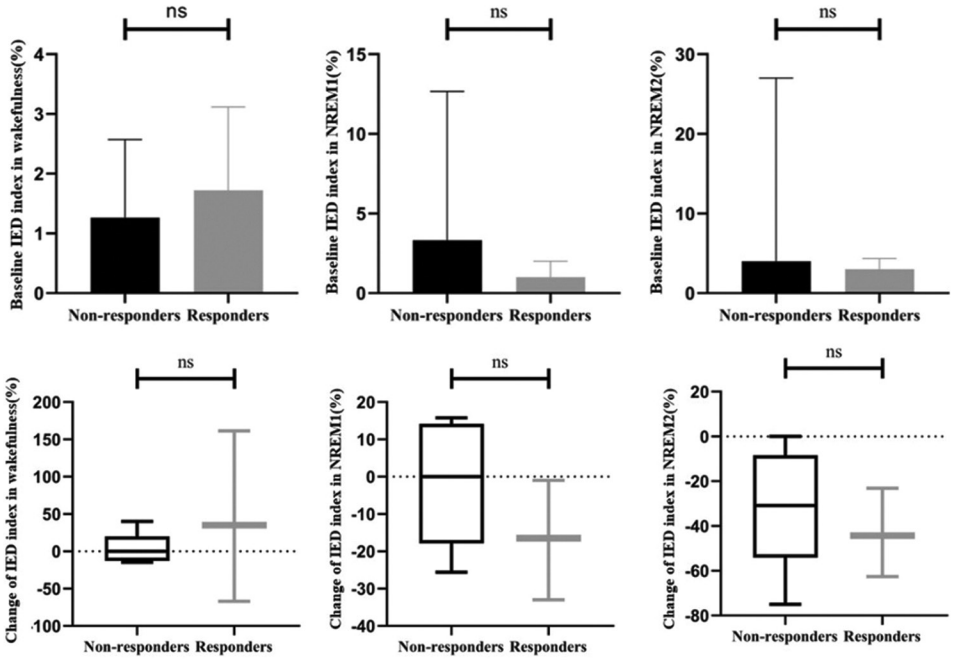

Figure 5. The comparison of the interictal epileptic discharge (IED) index between responders and non-responders to modified Atkins diet treatment. The three upper panels* depict the comparison of the baseline IED index between responders and non-responders, while the three lower panels show the comparison of the change of IED index between responders and non-responders. Non-normally distributed variables (baseline IED index in NREM1 and baseline IED index in NREM2) were expressed by medians and inter-quartile ranges and tested by the nonparametric Mann–Whitney test. Normally distributed variables were tested by independent *t*-test.
Abbreviations: NREM1: Non-rapid eye movement 1; NREM2: Non-rapid eye movement 2.

potentiating epileptiform discharges, leading to seizure recurrence or induction;[23] (ii) the reduction of serum concentration due to the interaction of KD with antiseizure drugs,[24,25] and (iii) the spontaneous fluctuation of seizure frequency. In our study, one patient exhibited acceptable compliance and stable urine ketones but still experienced seizure deterioration. We further analyzed the changes in epileptiform discharges and found an increase in the IED index during wakefulness in this patient. This observation led us to infer that the patient may be resistant to KD treatment. Even 1 year after discontinuing MAD, the patient continued to report worsening seizures. Analysis of the corresponding 2-h EEG identified seizure attacks during the sleep period. When compared to the EEG 3 months after MAD, the IED index during wakefulness increased, but the IED index during light sleep was challenging to calculate as a result of the disturbance caused by the seizure attack. Therefore, the seizure deterioration in this patient cannot exclude the possibility of spontaneous fluctuations in seizure frequency. The reasons become perplexing when seizures in patients worsen during MAD treatment. Assessing ASM serum concentration, conducting EEG, and implementing long-term follow-up may prove useful. In addition, determining when to stop MAD remains a doubtful question for these patients. International recommendations suggest that 3 months is the minimum time point to evaluate if KD treatment is effective. Should patients discontinue the diet after 3 months or immediately on observing worsening seizures? It is undeniable that more underlying mechanisms need to be identified to improve the efficacy of MAD treatment.

Previous studies indicated that 51% of KD-treated and 42% of MAD-treated patients discontinued the diet before study completion.[26] In our study, the retention rate of MAD at 3 months is 50%. The reasons for not initiating MAD include the strictly restrictive carbohydrate and fat intake, lack of social support, and expensive costs. In addition, although patients can benefit from KD, the long-term retention rate remains a rather low level. The question of how to improve the retention of KD remains to be solved. In our study, we found that appropriate and abundant diet education before patients initiate MAD can be necessary to improve the retention rate and adherence. Seven patients changed their minds and did not initiate MAD primarily due to inadequate understanding of MAD. The high-fat diet is not difficult to obtain. Moreover, using a ketogenic formula in the first month may be a good choice.[27] It is necessary to create comprehensive KD manuals, video lessons, and regular training.

As a high-fat, low-carbohydrate diet, the most common adverse effects may include gastrointestinal symptoms such as diarrhea, abdominal pain, vomiting, and constipation. However, the symptoms are mostly mild and can generally be managed and prevented with intervention.[15,28] Furthermore, hyperlipidemia is a common adverse effect of all types of KD therapy, but the lipid levels typically increase temporarily; they often remain within the normal range after 12 months.[29-31] The adverse effect rate in our study is 37.5%, but the symptoms were mild, and all could be managed with minimal intervention. No significant difference was found between serum metabolism indicators and MAD treatment, except for the level of total cholesterol. Thus, in agreement with previous studies, the safety of MAD treatment in adult patients is confirmed in the present study.

Previous studies have identified objectively that KD treatment has a positive impact on behavioral and cognitive function in children and adolescents with refractory epilepsy. The results include improved gross motor and adaptation, as well as decreased anxiety and depression mood.[32] However, the positive cognitive effects of KD treatment in adults have been reported subjectively by patients and their parents in previous studies, which include improved alertness and concentration. Our results showed that MAD treatment can improve the scores of the AVLT instant recall scale. However, we found no significant difference between MAD treatment on choice reaction time and visual searching task scale scores.

The KD treatment has been shown to significantly improve EEG epileptiform discharge activity in patients with drug-refractory epilepsy, leading to improved background rhythm in the occipital region[33,34] and a decreased IED index.[35,36] Our results demonstrated that MAD treatment significantly reduces the IED index in NREM2. However, whether these changes in the IED index predict the clinical efficacy of KD treatment is still under debate. A study has indicated a correlation between the reduction of epileptiform discharge activity and clinical seizure improvement.[35] However, similar to other studies,[37] we found no significant correlation between the change in the IED index and the clinical efficacy of MAD. This lack of correlation may be related to the small sample size of our study, and further confirmation is required by expanding the sample size.

At present, there is no unified conclusion regarding early predictive factors of KD efficacy. In our study, we found no predictive relationship between baseline EEG general features, baseline seizure frequency, changes in epileptic discharge activity, and the clinical efficacy of MAD. In addition, GPFA and GPT were included in the EEG characteristics for analysis. The GPFA was initially recognized as a characteristic discharge of Lennox-Gastaut syndrome and was often associated with axonal muscle tonic seizures, drug resistance, and poor prognosis, such as developmental retardation.[38] Now, it is observed not only in patients with epileptic encephalopathy but also in patients with generalized idiopathic epilepsy and serves as an EEG indicator of poor prognosis.[38,39] GPT was first discovered as a predictor of drug-resistant idiopathic generalized seizures by Sun *et al*. and confirmed by multiple studies.[40] In patients with refractory epilepsy, we aimed to explore whether the presence of GPT or GPFA is associated with poor clinical efficacy of KD. Interestingly, our results showed that three patients have GPT, two patients have GPFA, and they are all non-responders, while no GPT or GPFA was found in the responder group. Further meaningful insights may be gained through additional analysis with an expanded sample size.

The primary limitation of our study is the small sample size. It is possible that the observed results could represent a placebo effect or regression to the mean. Enhancing the accuracy and reliability of our findings would necessitate a larger sample size and a more extended follow-up period. A well-designed prospective randomized controlled study, incorporating comprehensive laboratory tests, global neuropsychological assessments, and EEG at baseline and key time points, would provide the most robust evidence. In addition, the absence of detailed neuropsychological tests pertaining to overall cognition function is a noteworthy limitation that might result in overlooking other positive results. It would be valuable to include global cognitive assessments and explore comorbidities such as anxiety and depression in more detail. Moreover, investigating the mechanisms underlying seizure worsening after MAD treatment is an avenue that warrants further exploration.

5. Conclusion

While KD has garnered recognition as an effective treatment for patients grappling with refractory epilepsy, the intricacies of its impact on epileptiform discharge activity remain unclear. The early clinical predictors and EEG characteristics indicative of KD efficacy warrant further exploration.

Acknowledgments

We are truly grateful to the patients and their family members.

Funding

This research was supported by the Beijing Hospitals Authority Clinical Medicine Development of special funding (Grant Number: XMLX202117).

Conflict of interest

There are no conflicts of interest to declare.

Author contributions

Conceptualization: Huixin Liu, Hongjuan Lu, Wei Sun
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Methodology: Huixin Liu
Software: Huixin Liu
Writing – original draft: Huixin Liu
Writing – review and editing: Huixin Liu, Wei Sun

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Ethics Review Board of Xuanwu Hospital, Capital Medical University (Ethics Number: 2022231). Written informed consent was obtained from all the participants and their guardians.

Consent for publication

Written permission was obtained from patients to publish their data.

Availability of data

The data are not publicly available due to privacy restrictions. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ACCSCIENCE PUBLISHING

Brain & Heart

MINI-REVIEW

Therapeutic potential of mesenchymal stem cells and their mechanisms of regeneration for cardiac diseases

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Abstract

Ischemic heart disease remains a major contributor to mortality and disability despite significant advancements in traditional treatments. This threat underscores the need for exploring innovative cell-based therapies. The analysis of various stem and progenitor cells' capacity to promote heart regeneration has led to encouraging outcomes in preclinical and clinical experiments. Mesenchymal stem cells (MSCs) have demonstrated the ability to contribute to heart regeneration through several pathways, including differentiation from the mesoderm lineage, immunomodulatory characteristics, and paracrine actions. In addition, their accessibility, maintenance, and capacity to replenish endogenous stem cell niches render them appropriate for cutting-edge research. This review outlines the robust mechanism underpinning MSC-based heart regeneration, presents the potential therapeutic uses of MSCs for ischemic heart disease, and highlights some preclinical findings.

Keywords: Mesenchymal stem cells; Exosomes; Cardiac diseases; Clinical trials; Regeneration

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Citation: Poomani MS, Radhakrishnan V, James SB, Muthan K, Subramanian V. Therapeutic potential of mesenchymal stem cells and their mechanisms of regeneration for cardiac diseases. *Brain & Heart*. 2024;2(1):2065. https://doi.org/10.36922/bh.2065

Received: October 18, 2023

Accepted: November 30, 2023

Published Online: February 13, 2024

1. Introduction

A cardiac disorder known as ischemic heart disease (IHD) is characterized by a decrease in the blood and oxygen flow in the heart. It is a major factor in cardiovascular diseases (CVDs) and may be the cause of myocardial infarction (MI) and heart failure. Heart failure is a condition that is on the rise and is prevalent in urbanized countries.[1] MI results from insufficient oxygen supply to the cardiomyocytes, leading to a switch from mitochondrial aerobic respiration to anaerobic glycolysis, causing nutrient depletion and reduced clearance of metabolic end products. Cardiomyocytes lose their function and structure and are the primary cause of ischemic conditions and heart failure.[2] Cell-based therapy as a method of regenerative medicine is one of the most promising disciplines in medicine. Mesenchymal stem cells (MSCs) are an optimal cell source for tissue regeneration due to their availability from sources such as bone marrow (BM), fat, and synovium. They can differentiate into diverse cell lineages tailored to specific biomedical needs.[3] This review concentrates on the application of MSCs and their paracrine effects in MI to reverse dysfunction. The analysis also explores clinical studies

that use this cutting-edge regeneration methodology. The simple isolation, expansion, and versatile *in vitro* multi-lineage potential of MSCs make them attractive therapeutic candidates in the field of regenerative medicine.

2. Mechanisms of MSC therapy in cardiac disease

MSCs were first discovered from BM by Friedenstein and his colleagues in 1976.[4] The BM, adipose tissue, and umbilical cord-derived MSCs have diverse capacities for immunoregulation and differentiation in CVDs. The properties of MSCs, including their activity and immunoregulatory potential, can be influenced by variations in culture conditions.[5] The International Society for Cellular Therapy has established criteria for MSCs, including being plastic adherent, expressing specific positive CD markers, and differentiating to adipocytes, chondrocytes, and osteocytes. When cultivated in the laboratory, MSCs exhibit three key biological traits that make them suitable for cell therapy: (i) The ability to differentiate; (ii) the secretion of trophic factors that support tissue remodeling; and (iii) immunoregulatory properties. MSC's exact mechanism of action on cardiac repair is still unclear.[6] However, there are specific, feasible mechanisms: (i) The ability to graft new cells and differentiate them into distinct cell types, such as cardiomyocytes;[7] (ii) adverse effects on cardiac repair through paracrine signaling/mediators of MSCs;[8] (iii) stimulation of native cardiac stem cells (CSC) to promote tissue growth and repair;[9] and (iv) promotion of neovascularization and immunomodulation.[10]

The numerous methods of in vivo transfer of MSC to improve the cardiac efficiency of some vital routes of administration are (i) transendocardial stem cell injection (TESI),[11,12] (ii) peripheral intravenous infusion,[13,14] (iii) catheter-based direct intramyocardial delivery,[15] and (iv) intracoronary infusion delivery.[16,17] Transendocardial injection of 20 – 100 × 10^6 MSCs yielded the most favorable outcomes compared to other methods in cardiovascular clinical trials.[18]

3. Paracrine effect, extracellular vesicles (EVs) and exosomes, and immunomodulatory effects of MSCs in heart disease

A comparison of the paracrine effect, EVs, and exosomes of MSCs is summarized in Figure 1. In addition to the cell-mediated immunologic response, paracrine substances secreted by the body have a range of beneficial effects in the myocardium, such as enhanced local angiogenesis, reduced cardiomyocyte mortality, low fibroblast activation, stimulation of cardiac stem cells, and decreased myocardial fibrosis.[19] Nakanishi *et al*. found that the expression of two cardiac progenitor genes, myosin heavy chain and atrial natriuretic peptide, was upregulated in the conditioned medium of MSCs. The migration and differentiation of cardiac progenitor cells were promoted by the paracrine effect of soluble substances.[20]

Exosomes and EVs are the membrane-restricted biological components employed in regenerative medicine. The expression of CD13, CD29, CD44, CD73, and CD105 in the secretome of EV from MSC diminishes the characteristics of the MSCs' origins.[21,22] Moreover, the coding mRNA of EVs contains transcription factors that control transcription, cell division, and immunomodulation.[23] Within the non-coding RNAs that prevent the release of EV-MSCs, they exhibit a distinct pattern.[21] This mRNA successfully prevents apoptosis in ischemic cardiomyocytes by downregulating the production of the Bcl-2 protein family subset, the p53-stimulated modulator of apoptosis.[24] Exosomes and MSCs were delivered with intramyocardial injection into acute MI to improve the milieu, minimize the inflammatory response, and improve cardiac function.[25] Host cells act as mediators for various immunomodulatory actions mediated by MSCs. After cardiac injury, the regeneration process is regulated by the clearance of cell debris, stimulation of local precursor cells, and regrowth of cardiac tissue to compensate for qualitative and quantitative changes in the vascular network, fibrotic scar formation, and inflammatory responses.[26] Anti-inflammatory M1 macrophages, soluble mediators such as prostaglandin E2, hepatocyte growth factor, indoleamine 2,3-dioxygenase, soluble HLA G5, heme oxygenase-1, transforming growth factor-1, and anti-inflammatory interleukin 10 (IL10) are well-known components in this process.[27] In the adaptive system, MSCs block the maturation of B cells and dendritic cells, dampen the proliferation of T helper (Th) cells and cytotoxic T cells, and stop the production of proinflammatory cytokines by T-cells. They also decrease the activating receptors of the natural killer cells in the innate system. This reduces the inflammatory response in mice's hearts following the start of MI the intravenous secretion of a protein induced by TNF-stimulated gene-6 (*TSG-6*).[28,29] It has been shown that modifying MSCs with different growth factors and cytokines improves vascularization and cardiac remodeling, decreases inflammation, and increases angiogenesis.[28]

4. MSCs in animal models for the treatment of MI

A list of clinical trials using animal models on mesenchymal-based stem cell therapy is presented in Table 1. *In vivo* tests

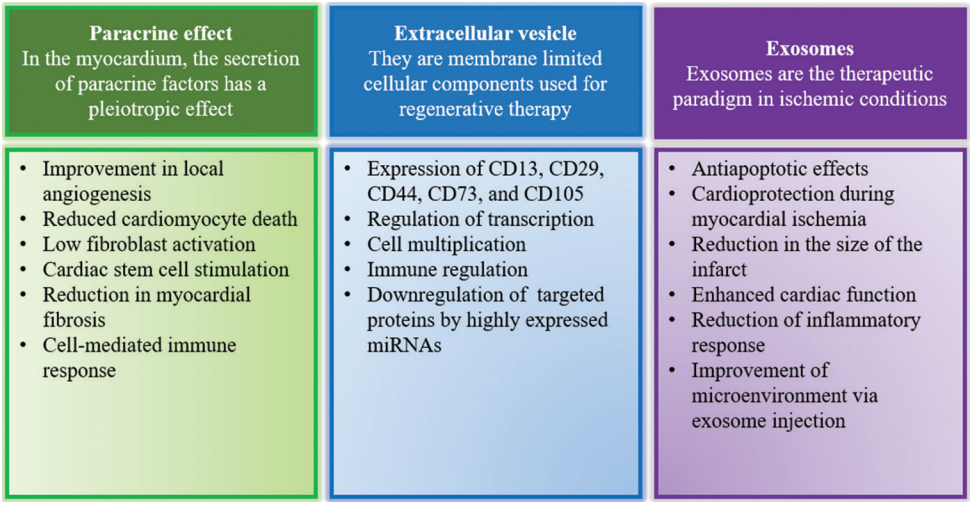

Figure 1. Comparison of therapeutic effects of mesenchymal derived exosomes, extracellular vesicles, and their paracrine effects.

Table 1. Summary of clinical trials in animal models

Animal model	Cell source	Condition	Method	Outcome	References
Rat	Adipose tissue-derived MSC	AMI	Transplantation	Acceleration of angiogenesis in the infarcted area after rat myocardial infarction and improvement of heart function	47
Rat	Human umbilical cord MSC	DCM	Intravenous injection	Improved cardiac function through induction of myogenesis and angiogenesis; also inhibits myocardial fibrosis	32
Pig	Allogenic BM MSC	AMI	Intramyocardial injection	Successful in intramyocardial engraftment and differentiation into a cardiomyocyte	48
Swine	BM magnetic-labeled MSC	AMI	Intracoronary infusion	Regenerated new myocardium and prevent remolding at 2-month follow-up	35
Swine	Allogenic adipose tissue-derived MSC	AMI	Intracoronary infusion	Increased cardioprotective and reparative mechanisms and better cardiac magnetic resonance-measured perfusion	49

Abbreviations: AMI: Acute myocardial infarction; BM: Bone marrow; DCM: Dilated cardiomyopathy; MSC: Mesenchymal stem cell.

on animal models of the specific disease are still required before those findings can be applied to humans. Due to their small size, ease of handling, low maintenance, and low cost, small animals such as mice, rats, and rabbits are commonly employed as models for studying CVDs. Orlic *et al.* experimented on female mice with acute MI (AMI), promoting cardiac regeneration.[30] Transplantation of BM-derived MSCs stimulated with 5-azacytidine led to differentiation into cells resembling cardiomyocytes and cardiac cells in the rabbit model of dilated cardiomyopathy (DCM).[31] Human umbilical cord-MSCs were used to treat the DCM rat model, which reduced fibrosis.[32] However, small changes in *in vivo* animal models have certain disadvantages. Therefore, animals such as pigs, porcupines, dogs, and sheep are used in scientific investigations.[33] Pigs' left ventricular ejection fraction (LVEF) is improved by intravenous injection of BM-derived MSCs.[34] Different studies found that 5 days after MI, an intracoronary injection of MSC cells into the pig heart increased LVEF and reduced infarct scar size.[35] Four weeks after MI, lambs were given allogeneic mesenchymal precursor cells and demonstrated neovascularization.[34]

5. Clinical trials with MSC

The initial clinical trial was conceived as a randomized study. In the prospective memory training to improve heart failure self-care (PROMETHUS) trial, autologous BM was injected into kinetic myocardial regions intramyocardially. In comparison to patients who received a placebo control, MSC-treated patients showed a lower scar mass ($-47.5 \pm 8.1\%$, $P < 0.0001$) and a greater LVEF ($+9.4 \pm 1.7\%$, $P = 0.0002$). In addition, they noted logical restrictions on scar contractility, perfusion, and size.[36] The safety of two

doses of allogeneic BM-MSCs in ischemic cardiopathy was investigated in the TRIDENT trial. A transendocardial injection of either 20 million or 100 million cells was given at random to 30 individuals. In all groups, the scar size decreased equally after a year of follow-up. There are inherent restrictions in clinical studies pertaining to cell dose, delivery time, administration method, processing of cells, and research follow-up. However, MSCs display potential for reducing scar size, augmenting local blood flow and contraction, stimulating vasculogenesis, reducing the effects of fibrosis in diseased tissue, and enhancing overall quality of life.[37]

6. Challenges and controversies surrounding MSC-based therapeutics for cardiac diseases

Some of the challenges involved in MSC-based therapeutics include the likelihood of cardiac arrhythmia and the differentiation of multipotent stem cells into undesirable noncardiac cells after implantation into heart tissue.[38] While MSCs can differentiate and mature into functional endothelial and cardiac cells, validation of this ability *in vivo* has yet to be completed, primarily due to the absence of specific cardiac markers for MSCs.[39] When a patient has an ischemic cardiac condition, the LVEF ranges from 2% to 4% and is not against the unique effects of the most widely prescribed pharmacological treatments. Hence, there is an optimistic expectation that progress in stem cell therapy, encompassing abundant cell sources, refined delivery techniques, and suitable preparation protocols, will propel cellular therapy for the treatment of CVD.[40]

7. Future perspectives for MSC in cardiac diseases

Various sophisticated techniques have been introduced to increase the efficacy of MSC. These approaches include (i) improving engraftment potential through genetic modification;[41] (ii) *in vitro* preconditioning to stimulate their differentiation;[42] (iii) pre-treatment of MSCs with growth factors or cytokines to enhance their paracrine properties;[43,44] and (iv) enhancing the effectiveness of cellular treatment of MI by facilitating MSC functional changes in collaboration with the host cardiac muscle.[45,46] It is thus expected that further studies will demonstrate the therapeutic potential of adult tissues' MSCs for ischemic MI.

8. Conclusion

Mesenchymal cells have garnered considerable interest in recent years due to their potential for the treatment of CVD. As mentioned previously, MSCs have unique properties that make them more potent therapeutic agents in cell-based treatments. MSCs play the role of regulatory cells that release mediating factors, promote growth factors, or entice cells to initiate restorative actions in injured tissues, in contrast to normal stem cells that mature into effector cells. It is because they offer an "off-the-shelf" treatment option allogeneic MSCs are especially interesting. In addition, they also avoid some of the drawbacks of using autologous cells. In summary, a number of preclinical investigations have yielded positive results. Nonetheless, large-scale, carefully planned, randomized clinical trials are necessary before MSC therapy can be used to treat the global health problem of IHD. Regardless of its therapeutic potential, stem cell biology is very promising.

Acknowledgments

We thank Dr. Ramachandran M.S., M.Ch., TIRM-TMCH for inspiring and guiding us to conceptualize MSC research in clinical application.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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ACCSCIENCE PUBLISHING

Brain & Heart

CASE REPORT

Percutaneous management of Lutembacher's syndrome: A case report

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Abstract

The definitive percutaneous management of Lutembacher's syndrome (LS) is a recognized alternative to surgery in selected cases. This intervention involves balloon mitral valvuloplasty (BMV) followed by device closure of the atrial septal defect (ASD). However, despite its recognition, certain challenges inherent to the procedure have not been highlighted in the majority of earlier case reports. The subject of the present case is a 30-year-old male diagnosed with LS who underwent definitive percutaneous treatment. The coexisting ASD required improvisation to facilitate balloon insertion across the mitral valve using the modified Inoue technique. Furthermore, the ASD device was deliberately oversized to prevent device embolization. This case highlights that percutaneous management of LS is not merely a combination of BMV and device closure procedures. Instead, the unique anatomic and hemodynamic features of LS should be considered when formulating treatment strategies for these patients.

Keywords: Atrial septal defect; Mitral stenosis; Modified Inoue technique; Balloon manipulation

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Citation: Uppal A, Sharma R, Sharma GL, Garg A. Percutaneous management of Lutembacher's syndrome: A case report. *Brain & Heart*. 2024;2(1):1701. https://doi.org/10.36922/bh.1701

Received: August 28, 2023

Accepted: November 15, 2023

Published Online: February 6, 2024

1. Background

The most common variant of Lutembacher's syndrome (LS), characterized by the combination of a congenital atrial septal defect (ASD) and acquired mitral stenosis (MS), has conventionally been treated through surgical intervention.[1] However, over the past three decades, a notable shift has occurred, as evidenced by several reports advocating for percutaneous management.[2-4] This approach involves percutaneous balloon mitral valvuloplasty (BMV) followed by ASD device closure, presenting itself as a seemingly simple and effective alternative.

The potential omission of the inter-atrial septal puncture step, facilitated by the presence of a concomitant ASD, may create the impression of a simplified procedure compared to conventional BMV. However, counterintuitively, the treatment of LS is more than just a combination of BMV and ASD device closure procedures. Recent reports underscore the unique anatomic and hemodynamic challenges faced by interventionalists in such scenarios, often requiring on-table improvisation of conventional techniques.[5,6] The current case report contributes to this body of knowledge by highlighting the unique challenges encountered when treating a young patient with LS.

2. Case presentation

A 30-year-old male presented with complaints of progressive dyspnea on exertion, easy fatiguability, and occasional non-exertional palpitations over the past 4 years, with a worsening of symptoms in the past 6 months. There were no reported orthopnea or paroxysmal nocturnal dyspnea episodes. On cardiovascular examination, notable findings included a loud S1, the presence of a wide fixed-split S2, a loud P2 component, a mid-diastolic murmur at the apex lacking pre-systolic accentuation, and a Grade 2 ejection systolic murmur in the second left intercostal space.

The 12-lead electrocardiogram indicated sinus rhythm, bi-atrial enlargement, right ventricular hypertrophy, and a right bundle branch block pattern. In addition, the chest X-ray revealed a straightened left heart border, a double atrial shadow sign, and borderline cardiomegaly with pulmonary venous congestion and dilated proximal pulmonary artery segments.

Two-dimensional transthoracic echocardiography (TTE) (Figure 1A-D) indicated findings suggestive of LS, including rheumatic MS with a planimetry-based mitral valve area of 1.0 cm^2, a mean transmitral gradient of 5 mmHg (severity of MS was masked by left atrium [LA] decompressing through ASD), trace mitral regurgitation, grossly dilated atria (right > left), ostium secundum ASD with a diameter of 12.5 mm, and mild tricuspid regurgitation with an estimated systolic pulmonary artery pressure of 50 mmHg. The MV commissures were free of significant calcification, and no significant subvalvular thickening was noted. These findings, along with adequate ASD rim margins, suggested an opportunity for definitive percutaneous management. After obtaining informed consent as per institutional guidelines, the patient underwent BMV, followed by percutaneous ASD device closure in the same sitting.

The patient received an oral dose of aspirin (325 mg) and clopidogrel (300 mg) 1 day before the procedure, in accordance with the guidelines.[7] Intravenous heparin was administered at an initial dose of 5000 IU after obtaining peripheral access, with a repeat dose given after 1 h to maintain the activated clotting time over 200 s (as the procedure lasted for an unexpectedly long duration). Right femoral venous access was secured, and a Mullin's dilator (8F sheath) was used to insert a 035" hydrophilic Terumo wire through the ASD into the LA. At this stage, the mean LA pressure was 6 mmHg, while the mean right atrium (RA) pressure was 3 mmHg. Next, the hydrophilic wire was exchanged with a pigtail (spring coil) wire, which was parked into the LA. The Mullin's dilator was then removed, and the SYM® valvuloplasty balloon-catheter assembly of size 26 mm was advanced over the spring coil wire following groin dilatation with a 14F dilator. On reaching the LA cavity with the balloon catheter assembly, we proceeded to remove the wire-straightener assembly. Subsequently, we used the J-shaper stylet in an attempt to

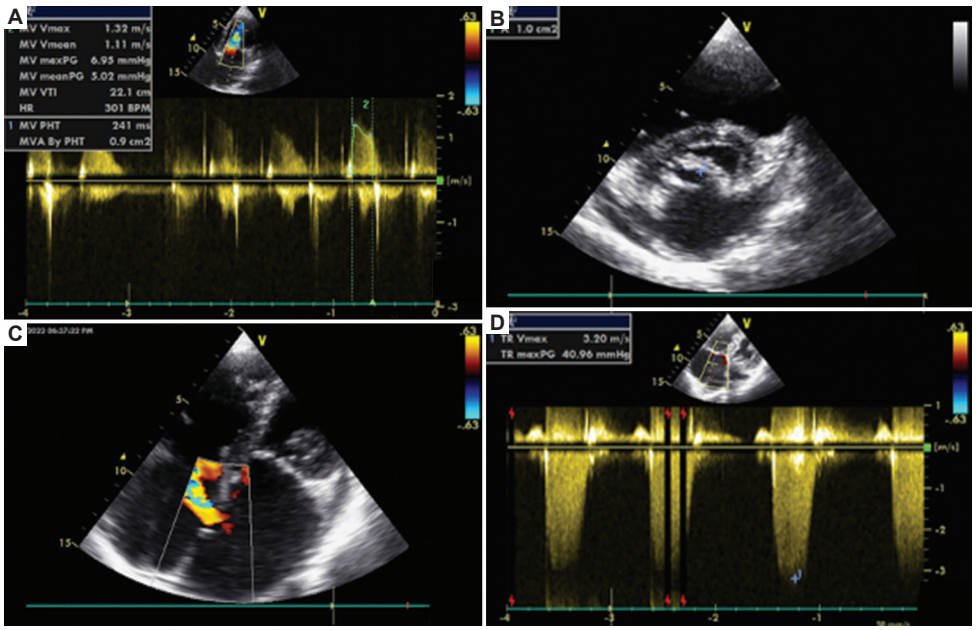

Figure 1. (A) Continuous wave Doppler tracing showing the mean gradient across MV at initial evaluation; (B) planimetry-based MVA calculation in the stenosed valve with fused commissures; (C) an ostium secundum ASD with the left to right shunt; (D) peak RV systolic pressure before procedure calculated from peak of the TR jet.
Abbreviations: ASD: Atrial septal defect; MV: Mitral valve; MVA: Mitral valve area; RV: Right ventricle; TR: Tricuspid regurgitation.

enter the left ventricle (LV) using the conventional method of anticlockwise turning of the catheter, aiming to position it across the MV (Inoue technique) in the right anterior oblique (RAO) view.

While executing this maneuver, our balloon-stylet assembly consistently veered into the RA through the ASD. This occurrence likely stemmed from the relatively smaller LA size in LS, compounded by the instability during catheter manipulation. The large inter-ASD, unlike in routine BMV cases, could not function as a stable pivot for the balloon catheter.

Consequently, we found ourselves repeating the aforementioned steps multiple times. Despite employing various techniques, such as reverse-loop entry and reshaping the stylet to form a large radius curve, we encountered persistent challenges in successfully crossing the MV. In response, we applied the modified Inoue technique,[8] where the valvuloplasty catheter was exchanged with a 6F Judkins Right (JR) catheter. The catheter was parked in the LA and its tip maneuvered to point towards MV in RAO view. We then crossed the MV with a Terumo 035" wire. Next, we advanced this wire across the aortic valve into the ascending aorta for maximum support (Figure 2A). The JR catheter was then advanced across MV, and Terumo wire was now exchanged with spring coil wire to prevent LV perforation during balloon advancement (Figure 2B). The JR catheter

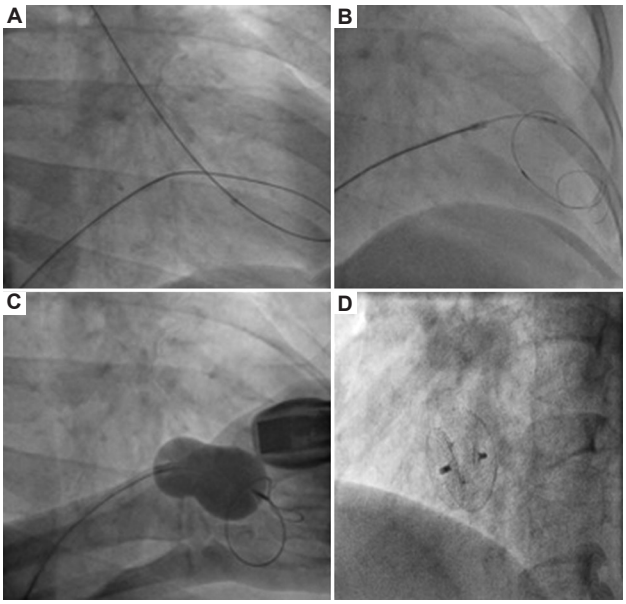

Figure 2. (A) 035" Terumo wire crossed across MV and AV and finally parked into the aorta for maximal stability; (B) SYM® balloons (size 26) being advanced across the MV over the spring coil wire parked in the LV cavity; (C) balloon dilatation of MV with SYM® balloon; (D) ASD device 16 mm post-deployment across ASD.
Abbreviations: ASD: Atrial septal defect; AV: Aortic valve; LV: Left ventricle; MV: Mitral valve.

was then exchanged with the balloon catheter, which was advanced across the MV into the LV over a spring coil wire, taking special care to remove the straightener only when at least two-thirds of the balloon catheter assembly was across the ASD. BMV was then performed with two serial balloon dilatations (increasing the contrast volume by 1 ml post-first inflation) (Figure 2C). More than a 50% reduction in LA pressure was achieved, along with TTE confirmation of bilateral MV commissure splitting. Next, the ASD closure was performed using the same 8F Mullin's sheath and a Lifetech Cera ASD occluder (16 mm) device (Figure 2D). Following ASD closure, the peak RV pressure, as estimated from the TR jet, decreased to 19 mmHg, and the mean transmitral gradient was down to <1.5 mmHg (Figure 3A and B).

The post-procedure recovery went smoothly without neurological or cardiac complications. The patient was discharged the next day and prescribed oral aspirin (75 mg) and clopidogrel (75 mg) once daily for 3 months, followed by oral aspirin (75 mg) alone for the following 3 months, after which the antiplatelet therapy was discontinued.[7] The patient has been on a 12-month follow-up. His exercise capacity has improved dramatically, and the mean transmitral gradient was less than 5 mmHg on subsequent TTE examinations, with no residual ASD shunt (Figure 3C).

3. Discussion

MS occurs in approximately 4% of patients with ASDs.[9] While the presence of ASD theoretically simplifies the process of BMV in LS, recent case reports have shed light on the unique challenges faced by interventionalists.[5,6]

First, the hemodynamic physiology in LS permits left atrial decompression, resulting in a smaller LA (with a larger RA) compared to isolated MS. This anatomical abnormality complicates the manipulation of the balloon to pass the MV.[10] Second, the substantial defect causes the balloon catheter to float freely, exacerbating its instability during maneuvers to cross the stenosed MV,[6] unlike in isolated MS, where the normal interatrial septum supports the catheter shaft, facilitating an acute curve with the balloon tip pointing toward the MV orifice.

Therefore, percutaneous intervention in LS goes beyond the mere combination of two individual procedures — BMV and ASD device closure. The unique anatomic and hemodynamic aspects of this condition should be thoroughly considered in advance, and the interventionalist must be well-versed in employing various techniques that facilitate balloon manipulation and entry across the MV. These techniques encompass the modified Inoue technique,[8] the use of balloon floatation catheters,[11] reshaping the stylet,[12] the over-the-wire (OTW)

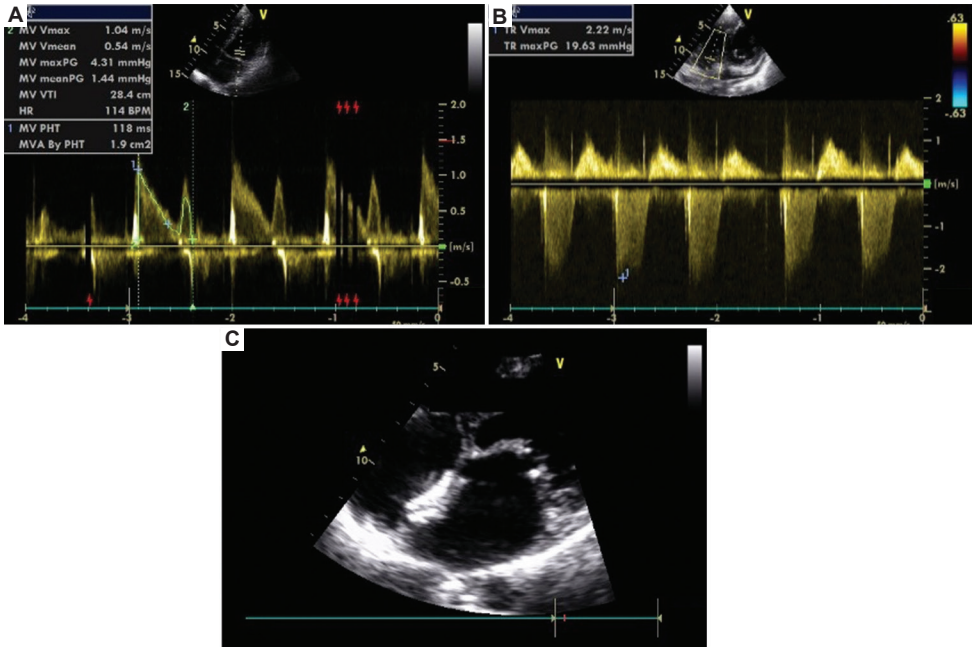

Figure 3. (A) Continuous Doppler tracing across MV post-BMV; (B) Peak RV systolic pressure post-procedure as estimated from the peak of TR velocity jet; (C) ASD device *in situ* at 3 months of follow-up.
Abbreviations: ASD: Atrial septal defect; BMV: Balloon mitral valvuloplasty; MV: Mitral valve; RV: Right ventricle; TR: Tricuspid regurgitation.

technique,[13] and retrograde balloon insertion through the arterial approach.[14] We employed the modified Inoue technique to achieve an optimal BMV result by leveraging our available hardware and the previous experience in treating such cases.

In the presence of good TTE images and ASD sizes <20 mm in diameter, we usually avoid trans-esophageal imaging during ASD closure, as was done in this case. As previously suggested by Bagga *et al.*,[6] we usually oversize the ASD occluder by at least 4 mm (instead of the routinely used 2 mm) in LS as the LA pressure is higher with co-existing MS and predisposes to device embolization.

The above case report, along with the previous publications, suggests that definitive percutaneous treatment in carefully selected LS cases is safe and effective, thereby reducing mortality and morbidity risks associated with cardiac surgery. Percutaneous treatment also decreases the physiologic trauma due to the thoracotomy scar and the length of hospital stay.[15] At the same time, the unique hemodynamic and anatomic aspects of co-existing MS and ASD should be given due consideration while planning definitive percutaneous intervention for these cases.

4. Conclusion

The adage "one plus one perhaps does not equal two" applies to the percutaneous management of LS. The apparent ease of performing BMV and ASD device closure in contemporary practice should not overshadow the unique challenges faced when combining these procedures in a patient with LS. Thorough pre-procedure planning, an in-depth understanding of the various balloon manipulation techniques to cross the MV, and precise sizing of the device for ASD closure are paramount. Neglecting these considerations may lead to potential catastrophes due to the underestimation of procedure difficulty.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Informed consent was taken from the patient for this publication. No patient-related information has been disclosed in the main manuscript and images.

Availability of data

Data used in this work are available from the corresponding author on reasonable request.

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ACCSCIENCE PUBLISHING

Brain & Heart

CASE REPORT

A novel pacing strategy for heart block in bilateral septal pacing: A case report

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Abstract

We present the case of a patient referred for conduction system pacemaker implantation after a complete block associated with transcatheter aortic valve replacement and reduced left ventricular function. In this case, we achieved bilateral septal pacing through the anodal capture of the right ventricular septum during bipolar pacing. This approach generated superior ventricular mechanical synchrony compared to left ventricular septum pacing (LVSP).

Keywords: Bilateral septal pacing; Left bundle branch pacing; Conduction system pacing

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Citation: He S, Zhao W, Dong X, *et al*. A novel pacing strategy for heart block in bilateral septal pacing: A case report. *Brain & Heart*. 2024;2(1):1670. https://doi.org/10.36922/bh.1670

Received: August 24, 2023

Accepted: November 21, 2023

Published Online: February 13, 2024

1. Background

Conduction system pacing (CSP) has been suggested as an alternative to address chronic right ventricular (RV) pacing-related complications. Left bundle branch pacing (LBBP), which involves the direct capture of the left bundle branch (LBB), offers an additional option for CSP with a relatively lower and stable capture threshold. However, the interventricular synchrony resulting from LBBP is not as optimal as with his bundle pacing due to a longer right ventricle activation time (RVAT).[1] In this report, we detail a case of complete heart block where successful bilateral septal pacing (BSP) was achieved, effectively mitigating RVAT. A narrower QRS of non-right bundle branch block (non-RBBB) morphology was observed when a bipolar pacing configuration was adopted in this case. This finding indicates that BSP was achieved with the capture of both aspects of the septum.

2. Case presentation

A 77-year-old male with a medical history of coronary artery disease, hypertension, hyperlipidemia, and severe peripheral artery disease was diagnosed with severe symptomatic aortic valve stenosis after presenting with Class III heart failure. Echocardiography revealed a depressed left ventricular ejection fraction of 38%. The initial electrocardiogram (ECG) showed an RBBB (Figure 1). Given the severity of his symptoms, transcatheter aortic valve replacement (TAVR) was recommended. Following valve deployment, a complete heart block was observed.

Subsequently, the patient underwent dual-chamber pacemaker insertion to address the heart block. A C315HIS sheath (Medtronic, Inc., Minnesota, USA) was introduced

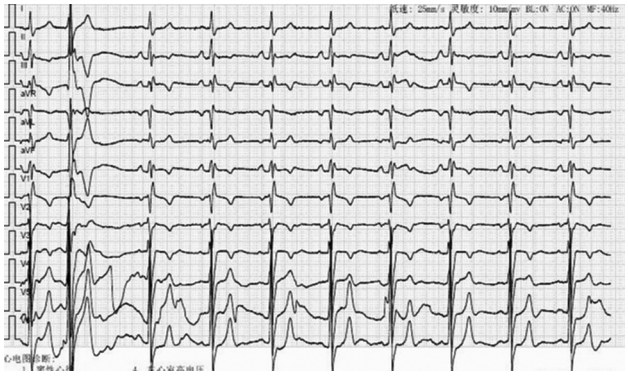

Figure 1. Baseline electrocardiogram indicating complete right bundle branch block.

into the right ventricle. A SelectSecure lead (Model 3830; Medtronic, Inc., Minnesota, USA) was then screwed into the RV septum. The pacing lead was maneuvered to the tagged area, in which unipolar electrode tip pacing demonstrated QRS complex with a "W pattern" in ECG lead V_1 and RS pattern in the inferior lead. As the lead was advanced, the W shape in lead V_1 changed to a QR pattern with a QRS duration of 158 ms (Figure 2). Notably, no discernible LBB potential was recorded. Threshold testing, utilizing unipolar pacing, revealed left ventricular septum pacing (LVSP) without LBB capture, consistent with the criteria established by Wu *et al.*[2] The pacing parameters were within acceptable ranges (pacemaker sensing: 10 mV; pacing threshold: 0.4 mV/0.4 ms, and pacing impedance: 580 Ω). An unexpectedly narrower QRS of non-RBBB morphology was noticed when a bipolar pacing configuration was adopted. This finding indicated that BSP was achieved with the capture of both aspects of the septum when bipolar pacing was performed.

ECG measurements were obtained using a multichannel recorder. Echocardiography was performed 1 week after the pacemaker implantation procedure to evaluate mechanical synchrony. The interventricular mechanical delay (IVMD) was measured as the time interval between the onset of QRS and the beginning of systolic waves of aortic and pulmonary ejections, using conventional Doppler.[3] Intraventricular dyssynchrony was evaluated using a Yu index, defined as the standard deviation of the time between the onset of QRS and the peak systolic velocity of tissue Doppler for 12 left ventricular (LV) segments (six basal and six middle) in apical triplane-mode (using a 4-Vprobe).[3] Septal-posterior wall motion delay (SPWMD) was measured through M-mode as the distance between the first maximum systolic inward motion of the septum and the maximum inward motion of the posterior wall.

Anodal capture using the ring electrode in the RV septum was observed using bipolar pacing at

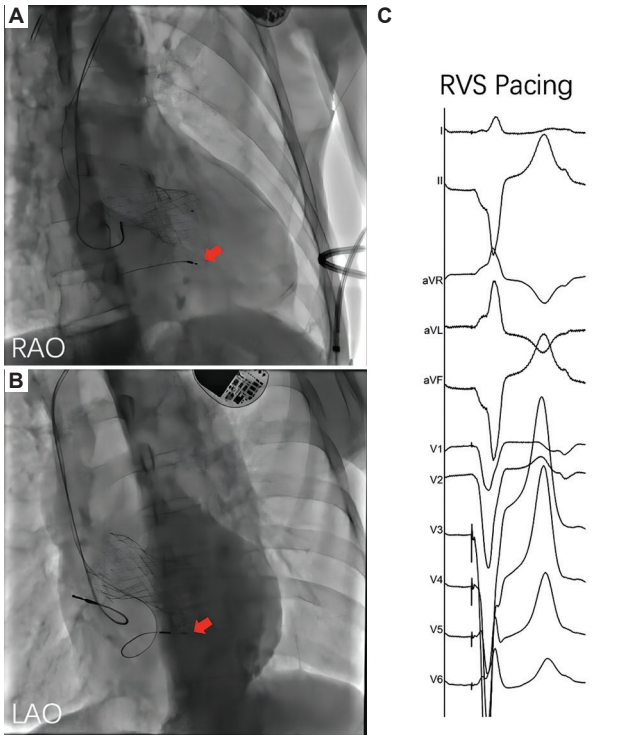

Figure 2. (A and B) X-ray images and (C) paced QRS during left ventricular septal pacing.
Abbreviations: LAO: Left anterior oblique; LVS: Left ventricular septum; RAO: Right anterior oblique.

2.0 V/0.4 ms, which resulted in favorable cardiac electrical and mechanical synchrony (Table 1 and Figure 3).

In comparison with LVSP, BSP led to a pronounced reduction in QRS duration. However, no R' was observed in ECG lead V_1 (QRS with RBBB pattern was not observed) during BSP (Figure 4). BSP improved the IVMD when compared with LVSP (Figure 5).

3. Discussion

The present case report is the first case description of BSP, showcasing a reduction in IVMD time compared to the LVSP. This unexpected achievement was realized through the right septal capture with an LVS lead. Our findings underscore the potential of BSP to attain optimal cardiac electrical and mechanical synchrony.

A notable complication frequently associated with TAVR is heart block, especially prevalent in patients with prior RBBB.[4] As documented in several studies, chronic RV pacing is linked to an increased risk of heart failure.[4] Recently, LBBP has emerged as a new pacing approach.[5] However, while LBBP produces a relatively narrow QRS complex with fast left ventricular activation, concerns persist regarding the presence of RBBB or even incomplete RBBB during pacing, leading to potential interventricular

Table 1. Analyses of cardiac electrical and mechanical synchrony

	Electrocardiogram					Echocardiography			
	QRSd (ms)	V_1[a]	LVAT (ms)	dRVAT (ms)	IVD (ms)	IVMD (ms)	Ts-SD (ms)[b]	PSD[c]	SPWMD (ms)
BSP	**114**	**QS**	**78**	-	-	**12**	**61.5±3.7**	**85**	**103**
LVSP	158	QR	82	126	42	43	96±2.0	101	132

Notes: [a]QRS morphology in lead V_1; [b]Ts-SD: Yu index (standard deviation of the time to longitudinal peak strain of 17 segments); [c]PSD: Peak strain dispersio7n.
Abbreviations: BSP: Bilateral septal pacing; dRVAT: delayed right ventricular activation time (the interval from the pacing to the peak R' wave upstroke in ECG lead V_1); IVD: Interventricular conduction delay (dRVAT-LVAT); IVMD: Interventricular mechanical delay; LVAT: Left ventricular activation time (the interval from the pacing to the peak R wave upstroke); LVSP: Left ventricular septal pacing; QRSd: QRS duration; SPWMD: Septal-posterior wall motion delay.

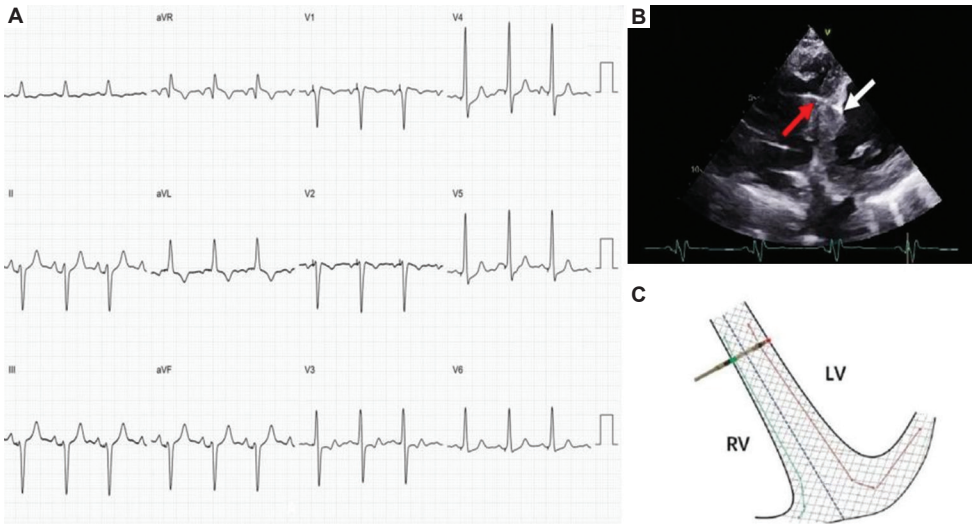

Figure 3. Electrocardiogram and schematic of activation pattern during bilateral septal pacing. (A) Paced QRS. (B) The red arrow indicates the ring of the pacing lead. (C) Schematic of the activation pattern.

dyssynchrony.[1,6] A study by Lin *et al.*6 demonstrates that pacing both left and right bundle branch areas with a single ventricular lead can further shorten QRS duration, effectively eliminating the RBBB pattern on ECG in a majority of patients.

Simultaneously pacing both the left and right bundle branch areas with a single ventricular lead can be challenging at times. In our patient, bipolar pacing with anodal capture of the RV septum could attenuate interventricular synchrony. Unipolar pacing at high output yielded a QRS morphology without any transitions before loss of capture, indicating left ventricular septal capture by the ring electrode without LBB capture. Bipolar pacing at 2.0 V/0.4 ms yielded a QRS morphology, eliminating the RBBB pattern and characterized by a relatively narrow QRS complex, which was attributable to RV septum capture by anodal. In our case, anodal capture by the ring electrode was possible only in the myocardium, as the initial ECG exhibited RBBB. BSP appeared to achieve more favorable cardiac electrical synchrony than LBBP in our patient.

Cardiac mechanical synchrony was notably enhanced during BSP, as demonstrated by echocardiography analyses. Cardiac synchrony is important for maintaining cardiac structure and function, and cardiac resynchronization has been identified as a valuable strategy for mitigating the risk of heart failure events.[7]

A previous study investigated the application of BSP in combination with coronary venous pacing for cardiac resynchronization therapy.[8] The study revealed that the combination of BSP with coronary venous pacing resulted in superior acute electrical synchronization compared to conventional cardiac resynchronization therapy. However, the study did not incorporate mechanical synchronization as a parameter. Echocardiography offers an accurate and convenient method for evaluating cardiac contraction and hemodynamics in real time without exposing the patient to radiation. In our patient, we employed IVMD as an index for interventricular synchrony and SPWMD as an index for intraventricular synchrony. Our observation revealed that LVSP distinctly prolonged IVMD and

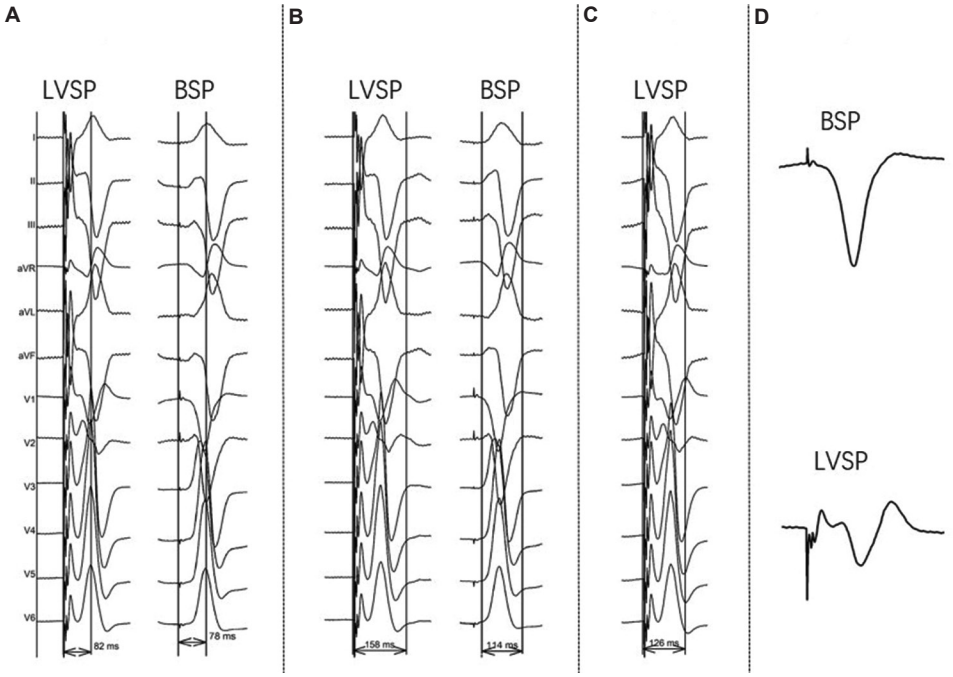

Figure 4. Electrocardiogram measurements. (A) Left ventricular activation time. (B) QRS duration. (C) Delayed right ventricular activation time. (D) QRS morphology in lead V_1.
Abbreviations: BSP: Bilateral septal pacing; LVSP: Left ventricular septal pacing.

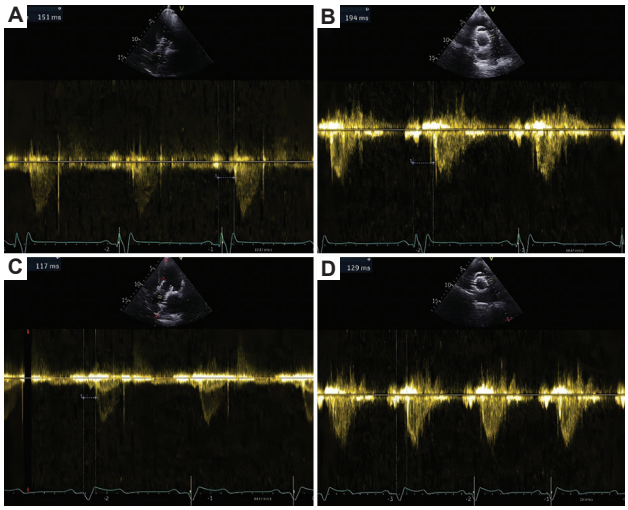

Figure 5. Interventricular mechanical delay during bilateral septal pacing (BSP) and left ventricular septal pacing (LVSP). The images show the time to onset of left ventricular ejection during LVSP (A) and BSP (C) and the time to onset of right ventricular ejection during LVSP (B) and BSP (D).

SPWMD, suggesting that LVSP induces interventricular dyssynchrony.

Several limitations warrant consideration in our study. First, our assessment of cardiac synchrony focused on LVS pacing, and we did not explore the synchronization during LBBP. However, existing animal and human studies suggested that both pacing strategies maintain comparable levels of electrical and mechanical activation in the left ventricle.[9,10] Second, our findings, based on ECG characteristics and echocardiography analyses, were limited by the absence of information on activation patterns. Further investigation should incorporate endocardial activation mapping to provide a more comprehensive understanding of cardiac activation during pacing. Third, the inability to achieve anode capture in certain cases, attributed to a small length of 3830 lead penetration into the septum or a high capture threshold, highlights the need for the development of new electrodes to overcome these challenges.

As previously stated, our study assessed synchrony during BSP and LVS pacing in a patient with a heart block. While we believe our findings have broader relevance, future studies involving a larger cohort will play a pivotal role in validating the reproducibility and generalizability of our findings.

4. Conclusion

To the best of our knowledge, this report is the first investigation into the mechanism underlying the phenomenon of a narrowed-paced QRS duration and reduced IVMD time during BSP. The observed maintenance of both inter- and intraventricular synchrony with BSP suggests it could represent a more physiologically advantageous pacing strategy for heart block.

Acknowledgments

The authors would like to thank the participating patients, as well as the colleagues and nurses who made this work possible.

Funding

None.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization: Jinrui Guo
Investigation: All authors
Resources: WanYu Zhao, Xiaoli Dong
Writing – original draft: Shanshan He
Writing – review & editing: Shanshan He, Jinrui Guo

Ethics approval and consent to participate

Not applicable.

Consent for publication

We obtained informed consent from study subjects for publishing their data.

Availability of data

The original data of the study are included in the article, and further inquiries can be directed to the corresponding author.

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ACCSCIENCE PUBLISHING

Brain & Heart

CASE REPORT

Completion Bentall procedure for a huge aortic root pseudoaneurysm after surgery for acute aortic dissection: A case report

Hisato Ito*, Satoshi Maruyama, Takato Yamasaki, Saki Bessho, Shuhei Toba, Yu Shomura, and Motoshi Takao

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Abstract

A 56-year-old man with a history of emergency ascending aortic and aortic valve replacement for acute type A aortic dissection 6 months previously developed a huge pseudoaneurysm arising from the sinus of Valsalva due to recurrent aortic root dissection. The patient urgently underwent the completion Bentall procedure with coronary artery reconstruction using interposing grafts. During surgery, the non-coronary sinus of Valsalva was repeatedly dissected and ruptured, where surgical glue was applied in the previous operation. The 25-mm REGENT mechanical valve® from the previous operation was left in place, and 2-0 bladed mattress sutures were circumferentially placed in the sewing ring of the prosthesis. A 28-mm Valsalva graft® was cut at the middle of its skirt portion, through which these sutures were passed and tied, and was seated to completely cover the valve cuff. The completion Bentall procedure is considered a feasible technique for reoperative aortic root replacement in patients with a prosthetic aortic valve following acute type A aortic dissection repair. It is important to accurately measure the outer diameter of the prosthetic valve to ensure proper fit of the graft and to minimize the risk of bleeding.

Keywords: Aortic dissection; Reoperation; Aortic root aneurysm; Aortic valve; Sinus of Valsalva

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Citation: Ito H, Maruyama S, Yamasaki T, *et al*. Completion Bentall procedure for a huge aortic root pseudoaneurysm after surgery for acute aortic dissection: A case report. *Brain & Heart*. 2024;2(1):2256. https://doi.org/10.36922/bh.2256

Received: November 15, 2023

Accepted: January 23, 2024

Published Online: February 16, 2024

1. Background

The completion Bentall procedure, a prosthesis-sparing operation, could be a good option in repeat surgery for aortic root pathology with a previously implanted prosthetic aortic valve.[1-3] We experienced a case of rupture and pseudoaneurysm formation of the sinus of Valsalva due to recurrent aortic root dissection in a patient with a history of emergency ascending aortic replacement and aortic valve replacement (AVR) for acute type A aortic dissection. We herein report the usefulness of the completion Bentall procedure for reoperative root replacement in patients with a prosthetic aortic valve following acute type A aortic dissection repair and the importance of proper size selection of a graft to minimize the risk of bleeding.

2. Case presentation

A 56-year-old man with a history of emergency ascending aortic replacement and mechanical AVR for acute aortic dissection 6 months before seeking medical

consultation from us complained of dull chest pain. Echocardiography showed a marked dilatation of the sinus of Valsalva, and a hyperechoic line suggesting a polyester fabric sheet inserted in the dissected aortic root in the previous operation. The prosthetic valve function was normal with mean transvalvular pressure gradient of 7 mmHg, and there was no paravalvular leakage (Figure 1A). Computed tomography revealed a huge pseudoaneurysm of the aortic root reaching beneath the sternum (Figure 1B and C). His blood pressure was 138/80 mmHg, and heart rate 77 beats/min on admission. The patient underwent an urgent operation. Before redo sternotomy, cardiopulmonary bypass was started with right femoral vein drainage with a 25 Fr venous reuptake cannula and right femoral artery perfusion using a 9-mm Dacron graft attached to the femoral artery. Then, the apex of the heart was exposed through the left 5th intercostal space, and a left ventricular apical vent was inserted, followed by systemic cooling. Redo sternotomy was performed during hypothermic ventricular fibrillatory arrest at systemic temperature of 22°C. After the redo sternotomy was completed, the mediastinal adhesions were dissected. The pseudoaneurysm was immediately entered, leading to a massive bleeding. Hypothermic circulatory arrest was induced, and the adhesion around the ascending aortic graft was removed. Following this, the graft was securely cross-clamped and transected. Then, systemic perfusion was resumed, and rewarming was started, followed by selective antegrade cardioplegic arrest. The right main pulmonary artery was lacerated due to the adhesion of the ascending graft, and it was repaired with a bovine pericardial patch.

The whole adventitia of the non-coronary sinus disappeared, and the polyester fabric which had been inserted in the false lumen and secured with BioGlue (CryoLife Europa Inc., Surrey, UK) in the previous operation was solely exposed (Figure 2A). Remnant BioGlue was seen around the polyester fabric. An approximately 10 mm intimal tear, which was not resulted from the previous operation, appeared in the non-coronary sinus. The proximal aortic suture line of the previous operation was intact. The 25-mm REGENT mechanical valve (Abbott, CA, USA) was left in place, and a total of 16 2-0 bladed mattress sutures were circumferentially placed in the sewing ring of the mechanical valve. A 28-mm Valsalva graft (Terumo Aortic, FL, USA) was cut at the middle of its skirt portion, through which these sutures were passed and tied, and was seated to completely cover the cuff of the mechanical valve (Figure 2C and D). The right coronary button was created and sutured to a 11-mm Dacron graft to approximate the intima and the adventitia because the aortic dissection involved the right coronary sinus. The left coronary sinus was free from aortic dissection, but the left coronary artery was difficult to mobilize due to severe adhesion. Therefore, an 11-mm graft was attached to the orifice of the left coronary artery using the inclusion technique. These grafts were attached to the Valsalva graft using the Piehler technique, through which the coronary arteries were reconstructed with graft interposition. Lastly, the Valsalva graft was anastomosed to the previous 26-mm ascending graft to complete the procedure. The patient was discharged home without complications.

3. Discussion

In patients with a history of AVR, aortic root dissection or root dilation may sometimes occur. However, this aortic pathology is not caused by the implanted aortic prosthetic valve. Dilatation or dissection of the aortic root constitutes

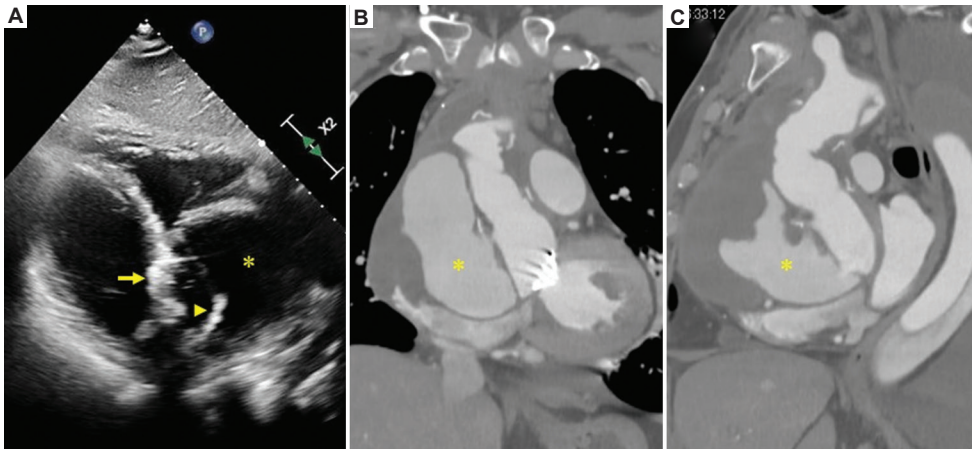

Figure 1. (A) Transthoracic echocardiography shows a markedly dilated aortic root (asterisk) with normally functioning mechanical valve (arrow). A hyperechoic line (arrowhead), suggestive of the polyester fabric sheet from the previous operation, is visible. Computed tomography reveals a large pseudoaneurysm (asterisk) in the coronal (B) and the sagittal (C) views.

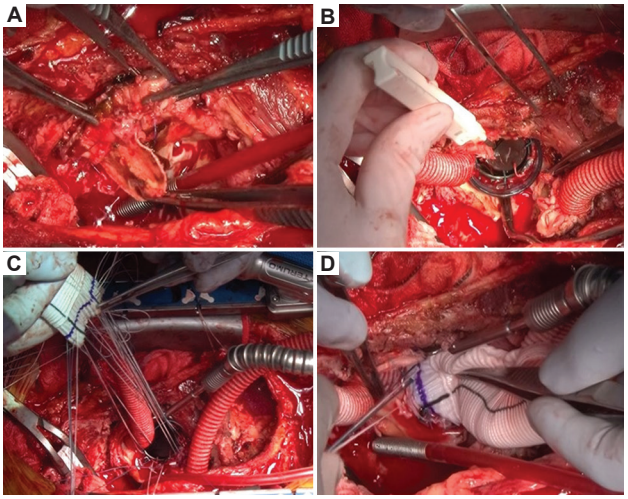

Figure 2. (A) The whole adventitia of the non-aortic sinus disappeared, and the polyester fabric was solely exposed. (B) The outer diameter of the 25-mm REGENT® valve was found to be slightly larger than that of a 33-mm cylindrical valve sizer. (C) A 28-mm Gelweave Valsalva® was cut at the middle of its skirt portion, through which these sutures were passed. (D) The graft was seated to completely cover the valve cuff.

most of the cases of aortic root reoperation after AVR, but pseudoaneurysm was less common in the literature.[3,4] There have been reports on pseudoaneurysms arising from the previous suture lines; however, the ones caused by aortic root rupture from repeat aortic dissection which was repaired with the completion Bentall procedure have rarely been reported. According to the three contemporary studies on reoperative aortic root surgery after previous acute type A dissection repair, 26 cases out of total 82 patients (31.7%) were operated on due to aortic root pseudoaneurysm. However, completion Bentall procedure was not implemented in any of these cases.[5-7]

In the previous operation, the dissected aortic layers of our patient had been attached with a polyester fabric inserted between the layers and secured with BioGlue. Although there have been reports suggesting a possible association between aortic dissection and an inflammatory reaction caused by BioGlue,[8,9] it remains unclear whether the recurrent dissection of the sinus of Valsalva might have been caused by BioGlue, as there were no findings attesting to the causal relationship.

In cases of a huge pseudoaneurysm, where massive hemorrhage is likely to occur during redo sternotomy and the degree of adhesion around the previous ascending graft is unknown, ventricular fibrillatory arrest along with hypothermic circulatory arrest offers a safe option for cross-clamping the ascending graft. In the setting of a mechanical valve, aortic regurgitation and subsequent ventricular overdistention caused by the continuous flow of cardiopulmonary bypass should be considered. An apical ventricular vent through small left thoracotomy may be an easy and safe option to address these issues.

If prosthetic valve replacement is not required, the completion Bentall procedure serves as an appropriate option, sewing a prosthetic graft to the sewing ring of the previously implanted prosthetic valve. If the graft is large enough to completely cover the prosthetic valve cuff, suture line reinforcement with the aortic wall remnant is not necessary to reduce the risk of bleeding, as previously reported.[1-3] The importance of measuring the true outer diameter of the prosthetic valve was highlighted in the literature.[10] In an *in vivo* setting, the outer diameter of a prosthetic valve can be slightly larger than that obtained from the commercially available chart. In our case, the outer diameter of a 25-mm REGENT valve is 33 mm according to the chart; however, it was found to be slightly larger than that of a 33-mm cylindrical valve sizer (Figure 2B). As a result, a 34-mm or larger graft was considered appropriate to completely house the prosthetic valve cuff, and a 28-mm Valsalva graft was chosen since its diameter is 36 mm at the midlevel of its skirt portion.

4. Conclusion

The completion Bentall procedure is considered a feasible technique for reoperative root replacement in patients with a prosthetic aortic valve following acute type A aortic dissection repair. It is important to accurately measure the outer diameter of the prosthetic valve to ensure proper fit of the graft and to minimize the risk of bleeding.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: Hisato Ito
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Supervision: Motoshi Takao
Writing – original draft: Hisato Ito
Writing – review & editing: Motoshi Takao

Ethics approval and consent to participate

A written informed consent was taken from the patient before participation.

Consent for publication

The patient consented to the publication of the images and data in this article.

Availability of data

Data that are essential for understanding the presented case are available in this article. Other data will be shared upon reasonable request to the corresponding author.

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ACCSCIENCE PUBLISHING

Brain & Heart

LETTER TO EDITOR

QTc interval and sympathetic tone in burning mouth syndrome

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Dear Editor,

The autonomic nervous system is closely related to the central nervous system and controls a variety of physiological functions. Increasing focus is being paid to the functionality of the neurocardiac axis and the crosstalk between brain and cardiac function. Brain function is enabled by the functional connectivity between different neural regions, which is referred to as a large-scale brain network. The functional brain networks consist of at least seven major networks: Sensorimotor system, visual system, limbic system, dorsal attention network, central executive network, default mode network, and salience network.[1] Alterations in brain network connectivity have been observed in a variety of diseases, and exploring therapies that modulate large-scale brain networks have been gaining traction in recent years. In this letter, I would like to share my perspectives regarding a paper on neural networks surgery by Yu *et al.*, which is an interesting read.[2] They described the application of brain network knowledge to the surgical treatment of cerebrovascular disorders from a neurosurgical perspective, and indicated that the treatment could protect the hubs that connect the nerves, and protect the connections between the hubs. The perspective of this paper can also be applied to our research area of chronic orofacial pain disorders of unknown origin. Therefore, we considered the aforementioned hubs play a pivotal role in patients with burning mouth syndrome (BMS), one of unexplained orofacial pain disorders, based on the measurement of QTc intervals as a marker related to the neurocardiac axis.

BMS is an intractable chronic pain disorder of unknown cause characterized by burning sensation without any organic abnormality in the oral mucosa. According to the International Classification of Headache Disorders, Third Edition (ICHD-3), BMS is defined as an oral burning sensation or dysesthesia that recurs daily for more than 2 h, without a clinically evident causative lesion, lasting more than 3 months.[3] In psychopharmacotherapy for BMS, low-dose amitriptyline is the first-line drug, which modulates serotonergic neurotransmission and stimulates the descending pain inhibitory pathway and the parasympathetic tone. In view of the recent findings by Yu *et al.*,[2] we undertook a study to investigate the autonomic nervous system of BMS patients, who were not instructed to take any pharmacotherapy to avoid the influence of psychotropic agents. During the first consultation, we obtained information such as the degree of pain as well as emotions associated with pain, and performed an electrocardiogram on the patients. This study was a single-center cohort study of consecutive patients who visited our hospital from April 2018 to March 2019. These patients were diagnosed with BMS according to ICHD-3 criteria, and consented to participating in the study. Exclusion criteria of this study are as follows: (i) Patients with obvious cardiac disease, (ii) patients

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Citation: Nagamine T, Watanabe T. QTc interval and sympathetic tone in burning mouth syndrome. *Brain & Heart*. 2024;2(1):2016. https://doi.org/10.36922/bh.2016

Received: October 11, 2023

Accepted: September 19, 2023

Published Online: February 13, 2024

taking medications that affect the QTc interval, and (iii) patients with comorbid psychiatric disorders or taking psychotropic medications. The degree of pain was examined using a visual analog scale (VAS), with 0 representing no pain and 100 representing the worst pain ever. The pain catastrophizing scale (PCS) was used to assess negative feelings associated with pain.[4] The QTc interval according to Bazett's formula was used as a measure of autonomic tone. Correlations between variables were examined using Spearman's rank correlation coefficient. All patients provided written informed consent for participating in this study. The personally identifiable information was not disclosed throughout the study to ensure anonymity and privacy. We were able to accumulate data from a total of 51 BMS patients: 11 males (21.5%) and 40 females (78.5%) with a mean age of 61.2 ± 1.6 years (mean ± SE). The VAS, PCS, and QTc at the first visit were 55.2 ± 3.2, 30.6 ± 4.1, and 417.8 ± 6.9 msec, respectively. The subjective degree of pain as measured by the VAS and destructive thoughts of pain as measured by the PCS were mildly correlated with a Spearman's correlation coefficient of 0.357 (P = 0.011; Figure 1). Interestingly, the VAS and QTc interval did not correlate (r = 0.087, P = 0.540; Figure 2), but the PCS and QTc interval showed a statistically significant correlation with a Spearman's correlation coefficient of −0.404 (P = 0.003; Figure 3).

Based on the results, both VAS and PCS values were high and moderately correlated with each other, although some patients had PCS values higher than VAS values and had negative feelings about pain. The recent functional imaging results of the participants, interpreted alongside the VAS, PCS, and QTc results, revealed a previously unidentified finding that some BMS patients have excessive sympathetic tone. Studies using functional connectivity magnetic resonance imaging have shown that individuals with unexplained pain such as BMS, fibromyalgia, back pain, and headache have an enhanced salience network activity, decreased functional connectivity between the default mode network and the executive control network, and decreased functional connectivity between the default mode network and the descending pain inhibitory pathway.[5] The salience network is strongly functionally coupled to the dopaminergic reward system of the basal ganglia and increases sympathetic tone in the hypothalamus. In our study, PCS was negatively correlated with the QTc interval, indicating that patients with destructive feelings of pain had a shortened QTc interval. Recent studies have shown that the QTc interval is associated with autonomic imbalance and tends to shorten with sympathetic tone.[6] The QTc interval reflects the degree of sympathetic tone under certain conditions, such as the absence of cardiac disease. Therefore, the negative correlation between PCS and QTc interval suggests that pain-induced emotion increases sympathetic tone. Patients with high PCS were

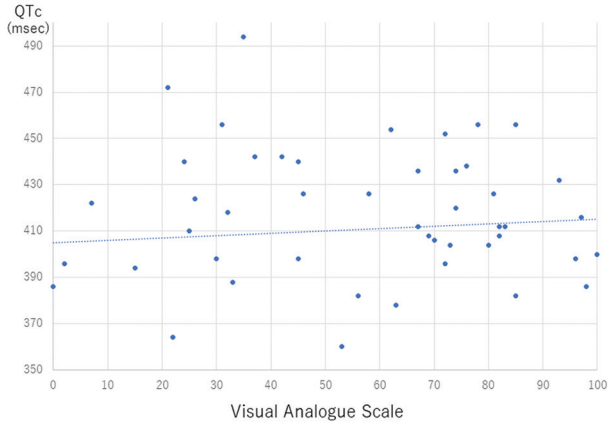

Figure 2. Correlation between QTc interval and visual analog scale.

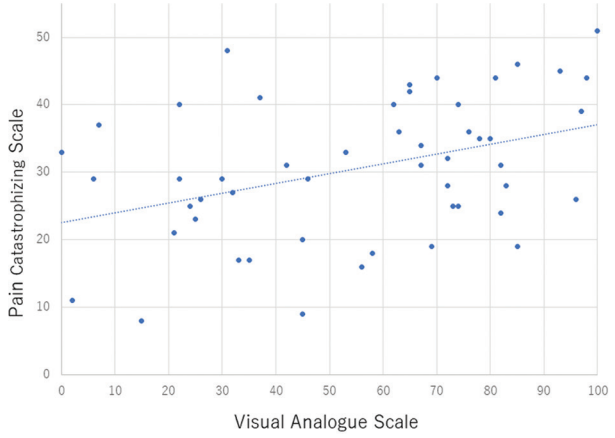

Figure 1. Correlation between visual analog scale and pain catastrophizing scale.

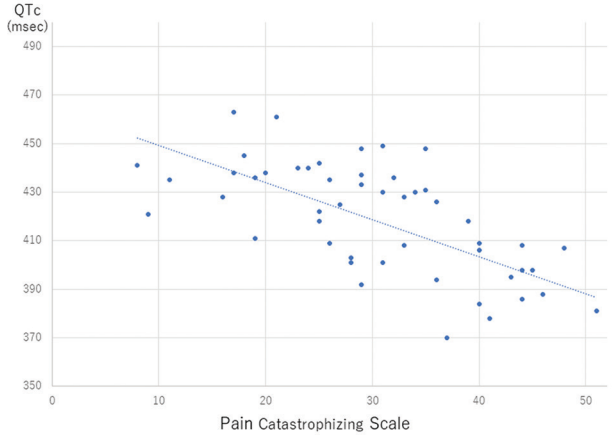

Figure 3. Correlation between QTc interval and pain catastrophizing scale.

considered to have an activated salience network and an activated anterior cingulate gyrus, which is one of the important hubs of the salience network and the center of the sympathetic nervous system. On the other hand, the VAS did not correlate with QTc interval, suggesting that pain itself does not tone the sympathetic nervous system. Energy-intensive organs such as the brain attempt to conserve energy in every way possible. Sympathetic tone with acute pain increases daily energy expenditure by 60%, while chronic pain increases energy expenditure by only 15%.[7] Chronic pain normally strengthens the functional connectivity between the somatosensory cortex and the default mode network, increasing the parasympathetic tone and decreasing energy expenditure.[8] Patients with high VAS but no shortening of QTc may have reduced energy consumption by decoupling pain from the sympathetic nervous system and connecting it to the parasympathetic nervous system. Although it is necessary to use the hub of the default mode network to link pain to the parasympathetic nervous system, the default mode network is also a network of self-recognition, which may also mean internalizing pain as one's own.

The VAS and PCS correlate only to some extent because the brain network may also be different for each individual BMS patient. The balance between the salience network and the default mode network is important for the autonomic nervous system to be stable. The salience network is controlled primarily by dopaminergic neurons, and the default mode network is regulated mainly by serotonergic neurons. Thus, pharmacotherapy such as aripiprazole (a dopamine D2 receptor partial agonist) and amitriptyline (a tricyclic antidepressant) may be effective for some BMS patients by modulating dopamine and serotonin.[9] However, a dose-response relationship is not seen with pharmacotherapy, and the therapeutic effect is only pronounced when high doses of pharmacotherapy, which are sufficient to induce antidepressant effect, are applied.[10] This indicates that drug therapies that target monoamines to alter neurotransmission may not necessarily improve the balance of the neural network because they are not site-selective and altering hub functions. As Yu *et al.* have shown, new treatments need to be considered for hub protection and network stability.[2] Network science provides theoretical and computational tools that can be used to understand simple concepts of human brain function; for instance, neuroimaging data analysis of functional networks of neurons emerges as a useful approach to enhancing our understanding of brain function.[11] New, network science-based psychopharmacological treatments that target key hub functions of pain circuits are warranted to alleviate the sufferings of BMS patients.

In conclusion, our study showed that drug-naïve BMS patients have increased sympathetic tone. The intraoral environment of BMS patients was worse than that of general dental patients.[12] Thus, it is necessary to examine whether there is a relationship between the oral condition of BMS patients and the sympathetic tone. Ultimately, treatments need to be designed, taking into account the neural networks of individual BMS patients and target key hub functions such as the basal ganglia and anterior cingulate gyrus. Further studies on brain networks and neurocardiac axis in these patients are needed.

Acknowledgments

I would like to thank everyone at the Department of Psychosomatic Dentistry, Tokyo Medical and Dental University (Prof. Toyofuku A.), for their generous cooperation in conducting this research.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Takahiko Nagamine
Investigation: Takeshi Watanabe
Methodology: Takahiko Nagamine
Writing – original draft: Takahiko Nagamine
Writing – review & editing: All authors

Ethics approval and consent to participate

All patients provided written informed consent to participate in this study. The study protocol was approved by the Ethics Committee of the School of Dentistry, Tokyo Medical and Dental University. The personally identifiable information was not disclosed throughout the study.

Consent for publication

Not applicable.

Availability of data

Data are available from corresponding author on reasonable request.

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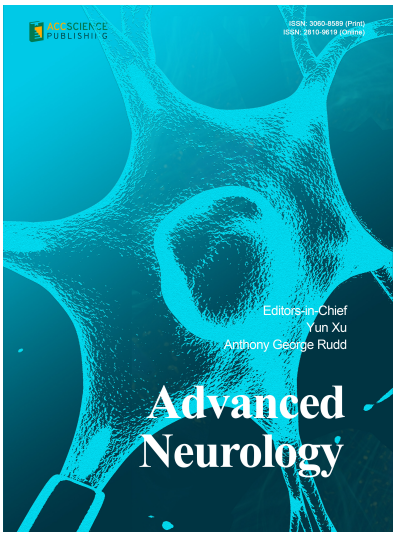

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