Role of exercise training in pulmonary hypertension: a review article

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ABSTRACT

Pulmonary hypertension is a cardiovascular disease with high mortality and morbidity affecting various aspects, including prognosis and quality of life. Limiting physical exercise in patients with pulmonary hypertension was initially suggested because it worsened the patient’s clinical condition. Recently clinicians have begun to focus on the role of physical activity in patients with pulmonary hypertension. Despite limitations of literature that describe the role of physical exercise in pulmonary hypertension, this paper is expected to provide an overview and the extent of implementing physical exercise in health centers. In our review, the data collection for eligible articles was conducted from 1st January 2011 until 4th January 2021 using the PubMed database undertaken English language. The search algorithm used in this paper is “Exercise” OR “Physical Activity” AND “Pulmonary Hypertension.” Manual search methods were also been used to find the topic-related articles. According to our synthesis of physical exercise in patients with pulmonary hypertension, it is safe to apply under the supervision of cardiac rehabilitation experts. Initial assessment, exercise capacity adjustment, and monitoring during physical exercise are essential to avoid adverse events during exercise. Regular physical exercise over 12 weeks can increase exercise capacity, improve quality of life, improve prognostic and life expectancy. Otherwise, the application of physical exercise under ten weeks does not always show significant results, and the application for less than eight weeks shows unsatisfactory results. In conclusion, the use of physical exercise in pulmonary hypertension has not been optimally utilized in cardiac rehabilitation centers.

Keywords: Cardiac rehabilitation, exercise, physical activity, pulmonary hypertension.

INTRODUCTION

The role of physical exercise in cardiovascular rehabilitation studies has thrived and increased nowadays. Since 1978, physical exercise as cardiovascular rehabilitation has been applied in Indonesia to reduce the impact of prolonged bed rest in patients with myocardial infarction. Furthermore, physical exercise is also applied to patients with other diseases with satisfactory outcomes. Then in 1980, the first National Rehabilitation Congress was held to discuss the early rehabilitation concept.\textsuperscript{1}

The role of physical exercise in the treatment of Pulmonary Hypertension (PH) has also been developed. In 2007, the American College of Sports Medicine (ACSM) introduced the term ‘Exercise is Medicine,’ aiming to make physical exercise a fundamental part of disease prevention and treatment for all patients. The concept of ‘Exercise is Medicine’ expectantly will increase the promotion of physical exercise, decrease physical inactivity, and reduce the severity of conditions in chronic disease.\textsuperscript{2,3}

The European Society of Cardiology (ESC)/European Respiratory Society (ERS) in 2015 recommended physical exercise under supervision in undergoing medical treatment Pulmonary Arterial Hypertension (PAH) patients, with the class of recommendation IIa and evidence level B.\textsuperscript{4} As time goes by, the role of physical exercise in PH patients has become apparent, proved by the latest ESC recommendations in 2020 for regular moderate-intensity exercise in patients with congenital heart disease (CHD), which is one of the sub-groups of PH, with the class of recommendation I and level of evidence B.\textsuperscript{5}

Although the role of physical exercise is increasing, the implementation of physical exercise in clinical practice still was not optimal.\textsuperscript{6} The percentage of physical exercise utilization in cardiac rehabilitation worldwide ranged from
20%-50% of total cardiovascular disease patients. Several factors that may reduce the optimization of physical exercise are inadequate cardiovascular rehabilitation availability, lack of resources, patient referrals to cardiovascular rehabilitation remain very low, difficult access and transportation to rehabilitation centers, patient social and economic status, and lack of motivation.

Physical exercise in PH was initially thought to aggravate the patient's clinical symptoms, caused right ventricle (RV) decompensation, and even lead to sudden death. Thus, PH patients are advised to limit activities and avoid doing physical exercise. However, recently, it has been discovered that physical exercise in PH patients provides impressive benefits, such as affecting exercise capacity, reducing the severity of clinical symptoms, affecting the psychological aspects, and improving quality of life. Along with the increasing recommendation class in physical exercise for PH patients, it is necessary to perform physical exercise optimally in various cardiovascular rehabilitation centers for satisfactory outcomes. Thus, this article will explain more about the role of exercise training in pulmonary hypertension.

**PHYSICAL ACTIVITY AND EXERCISE TRAINING**

According to the traditional definition, physical activity is defined as any movement of the body that occurs due to skeletal muscle contraction in producing energy expenditure. The current definition of physical activity leads to a holistic definition built by unique interests, emotions, ideas, attributes, and relationships when a person moves or acts. Shifting from the original concept that only focused on mechanical exertion, the new one is more complex and involves various aspects: attention, cognitive, affective, creative potential, and the environment. In line with these two concepts, the World Health Organization (WHO) defines physical activity as any movement produced by skeletal muscles, energy expenditure, and all movements, including any movements in leisure time. Physical activity is performed in a structured and repetitive manner that increases and maintains the components of physical health defined as physical exercise.

**PULMONARY HYPERTENSION**

Pulmonary Hypertension (PH) is a cardiopulmonary disease with high morbidity and mortality rate. Pulmonary hypertension is a chronic cardiopulmonary pathophysiological condition characterized by the progressive increase in pulmonary vascular resistance with Pulmonary Artery Pressure mean (PAPm) ≥ 25 mmHg at rest, assessed by Right Heart Catheterization (RHC). Besides, patients with PH are usually seen with a pulmonary capillary wedge pressure of ≤15 mmHg. More definitions about hemodynamic pulmonary hypertension were explained in table 1.

A study conducted 282 PH patients with WHO FC III (209; 74.1%), most of the subjects were idiopathic PAH (IPAH) (63; 33.4%), followed by PAH associated with congenital heart disease (CHD) (48; 17.0%), PAH associated with connective tissue disease (37; 13.1%), and PH due to chronic thromboembolic disease (proximal 61; 21.6%; distal 35; 12.4%). Congenital heart disease is included in the second PH group as ‘PH related to left heart disease (LHD)’ and divided into sub-groups as presented in Table 2.

**EXERCISE INTOLERANCE AND EXERCISE CAPACITY LIMITATIONS IN PULMONARY HYPERTENSION**

PH patients have high levels of disability, poor quality of life, and a low tolerance for physical exercise. Decreased pulmonary vascular distensibility causes an increase in pulmonary artery pressure during exercise and leads to physical intolerance. Decreased pulmonary blood flow and insufficient cardiac output do not meet the metabolic requirements for physical exercise. Exercise intolerance is also associated with decreased maximal oxygen uptake and anaerobic threshold, skeletal muscle abnormalities such as muscle atrophy, decreased muscle contractility, and impaired peripheral oxygen diffusion.

Patients with PH were sustaining muscle weakness and alterations of enzyme profiles and skeletal muscle morphology. These alterations impede muscle perfusion and peripheral oxygen delivery. Skeletal muscle in PH contains type I muscle fibers lesser than type II muscle fibers. Furthermore, alteration

### Table 1. Hemodynamic definitions of pulmonary hypertension.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>PAPm ≥ 25 mmHg</td>
<td>All</td>
</tr>
<tr>
<td>Pre-Capillary PH</td>
<td>PAPm ≥ 25 mmHg</td>
<td>1. Pulmonary Arterial Hypertension</td>
</tr>
<tr>
<td></td>
<td>PAWP ≤ 15 mmHg</td>
<td>3. PH due to lung disease</td>
</tr>
<tr>
<td>Post-Capillary PH</td>
<td>PAPm ≥ 25 mmHg</td>
<td>4. Chronic Thromboembolic PH</td>
</tr>
<tr>
<td></td>
<td>PAWP ≤ 15 mmHg</td>
<td>5. PH with unclear and multifactorial mechanisms</td>
</tr>
<tr>
<td>Isolated Post-capillary PH</td>
<td>DPG &lt; 7 mmHg and/or</td>
<td>2. PH due to left heart disease</td>
</tr>
<tr>
<td>(Ipc-PH)</td>
<td>PVR ≤ 3 WU</td>
<td>5. PH with unclear and multifactorial mechanisms</td>
</tr>
<tr>
<td>Combined Post-capillary and</td>
<td>DPG ≥ 7 mmHg and/or</td>
<td></td>
</tr>
<tr>
<td>pre-capillary PH (Cpc-PH)</td>
<td>PVR &gt; 3 WU</td>
<td></td>
</tr>
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<td></td>
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<td></td>
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</tbody>
</table>

CO=Cardiac Output; DPG=Diastolic Pressure Gradient (diastolic PAP-mean PAWP); mPAP=mean pulmonary arterial pressure, PAWP=pulmonary arterial wedge pressure; PH=pulmonary hypertension; PVR=Pulmonary Vascular resistance; WU=Wood Units
Table 2. Clinical classification of PAH associated with CHD.\textsuperscript{16}

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Eisenmenger’s syndrome</td>
<td>Includes all significant intra and extracardiac defects which begin as systemic co-pulmonary shunts and progress with time to a severe elevation of PVR and reversal (pulmonary to systemic) or bidirectional shunting, cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.</td>
</tr>
<tr>
<td>II. PAH associated with prevalent systemic</td>
<td>• Correctable\textsuperscript{a}</td>
</tr>
<tr>
<td>to pulmonary shunts</td>
<td>• Non-correctable</td>
</tr>
<tr>
<td></td>
<td>• Includes moderate to significant defects; PVR is mildly to moderately increased, systemic to pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.</td>
</tr>
<tr>
<td>III. PAH with small/coincident defects\textsuperscript{b}</td>
<td>Marked elevation in PVR in the presence of minor cardiac defects (usually ventricular septal defects &lt;1 cm and atrial septal defect &lt;2 cm of effective diameter assessed by echo), do not account for the development of elevated PVR. The clinical picture is very similar to idiopathic PAH. Closing the defects is contraindicated.</td>
</tr>
<tr>
<td>IV. PAH after defect correction</td>
<td>Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative hemodynamic lesions.</td>
</tr>
</tbody>
</table>

PAH=Pulmonary Arterial Hypertension, PVR=Pulmonary vascular resistance
\textsuperscript{a}With surgery or intravascular percutaneous procedure
\textsuperscript{b}The size applies to adult patients. However, in adults, the simple diameter may not be sufficient for defining the hemodynamic relevance of the defect and the pressure gradient, the shunt size and direction, and the pulmonary to systemic flows ratio.

Table 3. Physical exercise intensity.\textsuperscript{2}

<table>
<thead>
<tr>
<th>Intensity</th>
<th>VO2max (%)</th>
<th>HRmax (%)</th>
<th>HRR (%)</th>
<th>RPE scale</th>
<th>Training Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low intensity, light exercise</td>
<td>&lt;40</td>
<td>&lt;55</td>
<td>&lt;40</td>
<td>10-11</td>
<td>Aerobic</td>
</tr>
<tr>
<td>Moderate Intensity Exercise</td>
<td>40-69</td>
<td>55-74</td>
<td>40-69</td>
<td>12-13</td>
<td>Aerobic</td>
</tr>
<tr>
<td>High Intensity</td>
<td>70-85</td>
<td>75-90</td>
<td>70-85</td>
<td>14-16</td>
<td>Aerobic + Lactate</td>
</tr>
<tr>
<td>Very High Intensity</td>
<td>&gt;85</td>
<td>&gt;90</td>
<td>&gt;85</td>
<td>17-19</td>
<td>Aerobic + Lactate + Anaerobic</td>
</tr>
</tbody>
</table>

HRmax=maximum heart rate; HRR=heart rate reserve; RPE=rate of perceived exertions; VO2max=maximum oxygen consumption

Table 4. Relative benefits of pulmonary hypertension in rehabilitation services.\textsuperscript{19}

<table>
<thead>
<tr>
<th></th>
<th>Inpatient them home</th>
<th>Outpatient: PH specific</th>
<th>Outpatient: generic</th>
<th>Home</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cost</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Safety and</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>monitoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accessibility</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Pathophysiology of physical exercise in pulmonary hypertension

Looking further at the role of physical exercise in PH through remodeling blood vessels and right ventricle, the alterations of the inflammatory response, skeletal muscle, and oxidative stress.\textsuperscript{21} The process of blood vessels and right ventricles remodeling in PH patients occurs due to endothelial dysfunction, thickening of the tunica intima, and the muscle layer of the pulmonary blood vessels, discover hyperplasia and hypertrophy. It stimulates pulmonary vasoconstriction, increases pulmonary vascular resistance and right
ventricular afterload, leading to right heart failure. Physical exercise increases blood vessel density and affects the modulation of glycogen synthesis kinase (GSK-3β), a protein involved in angiogenesis and cardiac hypertrophy. Besides, the vasodilation induction increases the bioavailability of Nitric Oxide (NO), either by increasing NO production or by reducing NO inactivation. Through the increase in NO bioavailability, long-term physical exercise is expected to improve endothelial function. Another mechanism that plays a role in vasodilation by increasing the bioavailability of NO is the role of endothelium-derived hyperpolarizing factor and prostaglandins.23–25

Skeletal muscle dysfunction corrected by physical exercise causing alteration in muscle function, increasing type I skeletal muscle fibers while simultaneously decreasing the number of type II muscle fibers and increasing the anaerobic threshold of skeletal muscles, thereby increasing the patient’s physical exercise capacity.22–24 Inflammation also plays a role in pathogenesis by increasing vascular resistance.24 Interleukins, tumor necrosis factor (TNF), T lymphocytes, natural killer cells, and macrophages also induced inflammation in PH patients. A study shows the role of physical exercise in reducing inflammatory mediators of Th17 lymphocytes and IL-1β and IL-6.27

**EXERCISE PRESCRIPTION**

Exercise dose adjustment is an essential first step to prevent adverse events while undergoing a rehabilitation program, and eventually, physical exercise can be performed optimally. Therefore, adjusting the dose with the concept of ‘FITT’ (frequency-intensity- y-time-type) is based on the condition and risk factors from the initial assessment.24,26

The frequency of physical exercise shows the number of exercises practiced in a week. The recommendation for exercise frequency is 150 minutes per week. As the second factor, the exercise intensity should be determined carefully because it is related to the amount of energy expended. Moreover, exercise intensity plays a vital role regarding the risk of exercise that may increase while the rehabilitation program is running. Exercise intensity is defined as a maximal aerobic capacity percentage (VO max) or maximum heart rate (HRmax) percentage, HRmax = 220-ages. However, the latest calculation is discouraged because of bias possibility. Another calculation method used is the Karvonen formula, obtained by the resting heart rate added by the percentage difference between the maximum heart rate and the resting heart rate.5

The next factor is physical exercise, divided from the metabolic process; aerobic/anaerobic, or based on muscle work; isometric/isotonic, dynamic (concentric, eccentric) / static, continuous / interval, and the number of muscle groups involved.5 It is best to do a combination of aerobic and anaerobic physical exercises and supplemented with breathing exercises in PH. This combination is considered the best combination to improve the functional capacity in PH.20 Aerobic exercise could be practiced continuously or at intervals. However, interval exercise should only be applied in patients with stable heart conditions because interval training causes a higher heart workload.24,34

Physical exercise is recommended to start in PH by <50% VO2max with a shorter duration, about <30 minutes per session. Then exercise intensity should be increased according to the patient’s tolerance. As a maintenance dose of an ideal rehabilitation program, physical exercise can be practiced by moderate intensity, 50-75% VO2max, with a duration of 30-60 minutes, about 3-7 days per week for 10-12 weeks.25,35,36 High-intensity exercise in PH should be practiced with caution because it can aggravate shortness of breath, chest pain, and even syncope (Table 3).15

PH patients with restricted respiratory were advised to participate in the Constant Work Rate Cycling Endurance Test (CWRT), with the recommended peak load of 75%. The amount of the peak load could be adjusted to the duration of the exercise. Exercises practiced at 60% of the peak load should be done up to ≥10 minutes or vice versa; if physical exercise increases to ≥80% of the peak load, then the exercise should be done less than 10 minutes.10

Aside from aerobic exercise, resistance training using a maximum repetition unit (1RM) to measure exercise intensity is recommended at maximum repetitions of 5RM. The number of repetitions during exercise is inversely proportionate to the exercise intensity. Endurance training with exercise intensity of <20% 1RM is considered a type of aerobic endurance exercise. With exercise intensity higher than 20%, 1RM can cause a training effect due to hypoxia in the capillary muscle tissue by being squeezed during the muscle contraction. Exercise intensity between 30-50% 1RM with 15-30 repetitions achieved muscular endurance as the target. Moreover, exercise intensity of 50-70% 1RM with 8-15 repetitions used to train optimal strength.5

**Benefits of Exercise in Pulmonary Hypertension**

Physical exercise can improve cardiorespiratory fitness, functional status, and improve the clinical condition in PH with several estimations of exercise effects, influenced by the length of physical exercise that has been practiced.31 Studies measure that physical exercise duration for PH ranges from 8-15 weeks. Exercise practiced over 12 weeks show promising results. A randomized controlled trial (RCT) involving 30 participants over 15 weeks of exercise proves that physical exercise tolerates well in PH. Physical exercise increases peak oxygen consumption, anaerobic threshold value, increases WHO functional class (FC), enhances workload capacity, and improves the quality of life compared to the control group.32 Another study discusses the benefits of physical exercise over 15 weeks30,31,34 and over 12 weeks of physical exercises showed significant changes in exercise capacity, 6MWT, VO2max, WHO functional class, quality of life, improves right ventricular function, oxygen pulse, heart rate, systolic blood pressure, reduces carbon dioxide output, lowers type II muscle fibers, improves prognosis and increases 1-, 2-, 3-year of life expectancy.35,36

Another study with a shorter period of physical exercise, for ten weeks, did not always show satisfactory results. Several studies showed increases in the distance of the 6-minute walking test, cardiorespiratory function, physical activity, and the quality of life; but showed...
reduced fatigue symptoms.\textsuperscript{35-37} However, a cohort study conducted on 18 women with a sedentary lifestyle performing vigorous aerobic exercise training (AET) for ten weeks found no significant effect of AET on systolic or diastolic function. Nevertheless, AET plays a role in reducing afterload and maintaining left ventricular diastolic function.\textsuperscript{38}

Studies over an even shorter period, eight weeks, have shown unsatisfactory results. The study comparing physical exercise in 30 participants in PAH under direct supervision and independently at home found no significant differences between the two groups.\textsuperscript{39} Moreover, a study that assessed the effect of breathing exercises for eight weeks in PH showed no significant improvements in respiratory function, physical activity, functional physical exercise capacity, and quality of life.\textsuperscript{39} These occurrences conceive due to the study's relatively short duration and the limited number of participants. Further studies with a more extended period and a more significant number of participants are needed.

The exercise program in PH should be started before the patient returns from hospitalization to provide optimal benefits and exercise safety. Furthermore, the physical training program should be maintained during outpatient care as well. It provides education to practice physical exercise appropriately. Further, the exercise should practice independently at home, following the direction of the rehabilitation expert.\textsuperscript{40} In table 4, several benefits of pulmonary hypertension in rehabilitation services were explained from different aspects briefly.

SAFETY AND ADVERSE EVENTS

The safety and risk of adverse events during physical exercise as a rehabilitation program for PH patients have been studied. Based on a meta-analysis that involves 16 studies and 469 participants evaluating the safety of physical exercise in PH, physical exercise is safe enough to be applied in PH. The physical exercise presented well tolerated the incidence of adverse events during exercise was found of 4.7% of the subjects. Several adverse events in this study are dizziness, presyncope, syncope, palpitations, hypotension, or oxygen desaturation. Furthermore, no significant adverse events were found, such as clinical symptoms worsening, right heart failure symptoms occurrence, or sudden death among the participants during the training period. The adverse events rate in the physical exercise group was reported much lower compared to the pharmacotherapy group.\textsuperscript{18}

Furthermore, a cardiopulmonary exercise trial study of 16 patients with Idiopathic Pulmonary Arterial Hypertension (IPAH) and ten healthy participants, evaluating the safety level of physical exercise through the immunity and inflammation point of view. According to the study, physical exercise is considered safe to apply in IPAH.\textsuperscript{27} Moreover, a study enrolled 183 PH patients with PAH, chronic thromboembolic PH (CTEPH), and PH associated with respiratory disease or LHD, been practicing physical exercise for three weeks at the hospital and 15 weeks at home. The study considered the low intensity of physical and breathing exercises as safe to practice under intensive supervision. The study also suggested physical exercise as an adjunctive therapy. The adverse events presented in this study of 13% of patients include presyncope events, syncope, and respiratory infections.\textsuperscript{34}

Although in a small percentage, there are still possibilities of adverse events during physical exercise if the physical exercise exceeds the patient's training capacity.\textsuperscript{5,28} Several adverse events during physical exercise reported by various studies are dizziness and desaturation, and the worst adverse event is sudden cardiac arrest\textsuperscript{25} presyncope, syncope, hypotension and arrhythmias such as supraventricular tachycardia\textsuperscript{34}, and fatigue.\textsuperscript{20}

In CHD as a sub-group of PH, shunts left to right occurred caused excess volume/pressure in the right ventricle, for example, in atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA). Furthermore, the excessive and continuous increase in pressure will reverse the shunt direction, increasing pulmonary vascular resistance, called Eisenmenger syndrome. PH patients with CHD are currently safe to practice moderate-intensity physical exercise, as regular physical exercise, even some PH patients with corrected CHD are reported to be sports athletes with competitive exercises. The incidence of sudden death in PH patients with CHD is infrequent, ranged in <0.1% per year, with a sudden death rate while doing physical exercise around 8%. Maintaining the safety of physical exercise is necessary to evaluate the athletes with PH related to CHD periodically.\textsuperscript{5}

It concluded that physical exercise could be used as an adjunctive treatment strategy aside from pharmacological therapy. Physical exercise is considered safe and effective as a part of the cardiac rehabilitation program, especially in patients with chronic cardiopulmonary conditions, including PH patients.\textsuperscript{4,18}

WHEN TO STOP PHYSICAL EXERCISE

As a part of the cardiac rehabilitation program, patient monitoring is necessary to perform during physical exercises. Several adverse events were presented during exercise, including desaturation, syncope, chest pain, arrhythmias, or dizziness. So far, no specific standard has established when to stop or when to extend the physical exercise. However, it is suggested to gradually decrease the exercise intensity when the oxygen saturation level decreases to <85-90%, followed by the heart rate increase to >120-130 beats/minute. Furthermore, when the physical condition deteriorated by increasing exercise intensity, the patient should stop exercising. For example, when the patient starts to experience hypotension or a sense of discomfort.\textsuperscript{51}

CONCLUSION

Physical exercise as a rehabilitation program in PH is considered safe to apply, and it is recommended to practice regularly under cardiac rehabilitation expert supervision. It is necessary to adjust the dose against the patient's initial risk assessment. Physical exercise can improve the clinical condition of PH patients, regulate the patient's physiological and psychological aspects, increase exercise capacity, improve muscle function and strength, reduce the severity of patient clinical symptoms, reduce anxiety and
depression, and also improve the quality of life. The utilization of cardiac rehabilitation is expected to be further intensified by the advancing role of physical exercise in PH.

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**Author Contribution**

All authors contributed to the creation of this review article.

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We acknowledge all authors who shared with us their valuable work experiences.

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