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Review

Future Perspectives for Management of Stage A Heart Failure

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Patients with Stage A heart failure (HF) show no HF symptoms but have related comorbid diseases with a high risk of progressing to HF. Screening for comorbid diseases warrants closer attention because of the growing interest in addressing Stage A HF as the best means of preventing eventual progression to overt HF such as Stages C and D. The identification of individuals of Stage A HF is potentially useful for the implementation of HF-prevention strategies; however, not all Stage A HF patients develop left ventricular (LV) structural heart disease or symptomatic HF, which lead to advanced HF stages. Therefore, Stage A HF requires management with the long-term goal of avoiding HF development; likewise, Stage B HF patients are ideal targets for HF prevention. Although the early detection of subclinical LV dysfunction is, thus, essential for delaying the progression to HF, the assessment of subclinical LV dysfunction can be challenging. Global longitudinal strain (GLS) as assessed by speckle-tracking echocardiography has recently been reported to be a sensitive marker of early subtle LV myocardial abnormalities, helpful for the prediction of the outcomes for various cardiac diseases, and superior to conventional echocardiographic indices. GLS reflects LV longitudinal myocardial systolic function, and can be assessed usually by means of two-dimensional speckle-tracking. This article reviews the importance of the assessment of subclinical LV dysfunction in Stage A HF patients by means of GLS, and its current potential to prevent progression to later stage HF.

Key words: Stage A heart failure, Left ventricular longitudinal myocardial function, Global longitudinal strain

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Introduction

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) classification describes stages of heart failure (HF) development as Stages A to D based on structural changes and symptoms[1-3]. Whereas the New York Heart Association (NYHA) classes focuses on exercise capacity and the symptomatic status of the disease, this HF classification emphasizes the development and progression of the disease and can be used to describe individuals and populations. Patients with Stage A HF show no HF symptoms but have related comorbid diseases with high risk of progressing to HF, such as hypertension, diabetes mellitus (DM), obesity, hypercholesterolemia, and metabolic syndrome, in addition to a history of using cardiotoxins, or a family history of cardiomyopathy. The absolute mortality rate for HF remains approximately 50% within 5 years of diagnosis, although survival has improved[4]. A population cohort study reported that 5-year survival rates for Stages A, B, C, and D HF were 97%, 96%, 75%, and 20%, respectively[5]. Screening for comorbid diseases warrants closer attention because of the growing interest in addressing Stage A HF as the best means of preventing eventual progression to overt HF such as Stages C and D. Prospective epidemiologic studies have identified risk factors and risk markers for HF development. In addition, the identification of individuals with Stage A HF is potentially useful for the implementation of HF prevention strategies. It is not clear yet whether all Stage A HF patients or only those at high risk of developing HF should be screened using serial noninvasive assessment for detection of the beginning of left ventricular (LV) dysfunction such as seen in Stage B HF. Therefore, Stage A

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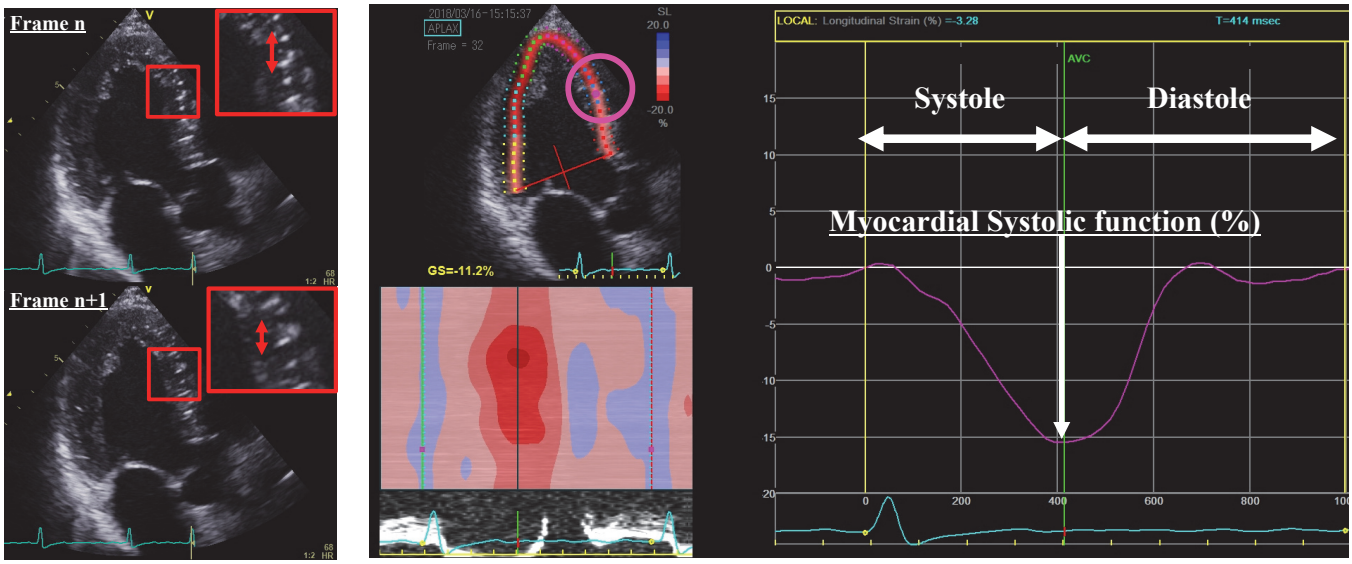

Fig. 1. Diagram of speckle tracking strain derived from two-dimensional long-axis echocardiographic images. Information about myocardial strain is generated by changes in speckles from frame to frame. Strain is calculated as the change in length divided by the original length and expressed as a percentage.

HF requires management with the long-term goal of avoiding HF development; likewise, Stage B HF patients are ideal targets for HF prevention. These individuals with prevalent cardiovascular diseases but without overt symptomatic HF include the majority of patients whose hearts are undergoing progressive maladaptive cardiac remodeling, which leads to HF. These silent abnormalities may lead over time to symptomatic LV dysfunction; however, such progression may be positively affected by early treatment. Although the early detection of subclinical LV dysfunction is, thus, essential for delaying progression to HF, the assessment of subclinical LV dysfunction can be challenging.

This article reviews the importance of the assessment of subclinical LV dysfunction, and LV longitudinal myocardial systolic dysfunction in particular, in Stage A HF patients, its current potential and future perspectives for the management of such patients.

Speckle-Tracking for Assessment of LV Longitudinal Myocardial Systolic Function

Echocardiography plays a pivotal role in the quantification and early detection of LV structural findings. However, global longitudinal strain (GLS) as assessed by speckle-tracking echocardiography has recently been reported to be a sensitive marker of early subtle abnormalities of LV myocardial performance, helpful for the prediction of outcomes for various cardiac diseases, and superior to conventional echocardiographic indices such as LV ejection fraction (LVEF), mitral inflow E and mitral e' annular velocities ratio (E/e')[6-10]. GLS reflects LV longitudinal myocardial systolic function, and can be assessed usually by means of two-dimensional speckle-tracking, while speckle-tracking is a post-processing computer algorithm that uses routine grayscale digital images[7]. Although several manufacturers have devised various speckle-tracking echocardiographic approaches, the basic approach is similar. Briefly, routine grayscale digital images of the myocardium contain unique speckle patterns. A user-defined region of interest is placed on the myocardial wall, and within this region of interest, the image-processing algorithm automatically subdivides regions into blocks of pixels by tracking stable speckle patterns. Then, subsequent frames are analyzed automatically by searching for new locations of the speckle patterns within each of the blocks by means of correlation criteria and the sum of absolute differences (**Fig. 1**). The shifts in location of these acoustic markers from frame to frame representing tissue movement provide the spatial and temporal data used to calculate velocity vectors. Temporal alterations in these stable speckle patterns are identified as moving farther apart or closer together and create a series of regional strain vectors. Strain information is not dependent on the Doppler angle of incidence, which makes the analysis of longitudinal strain possible. GLS is then determined as the averaged peak longitudinal strain of 18 LV segments from the three standard apical views, and is expressed as an absolute value (**Fig. 2**)[11].

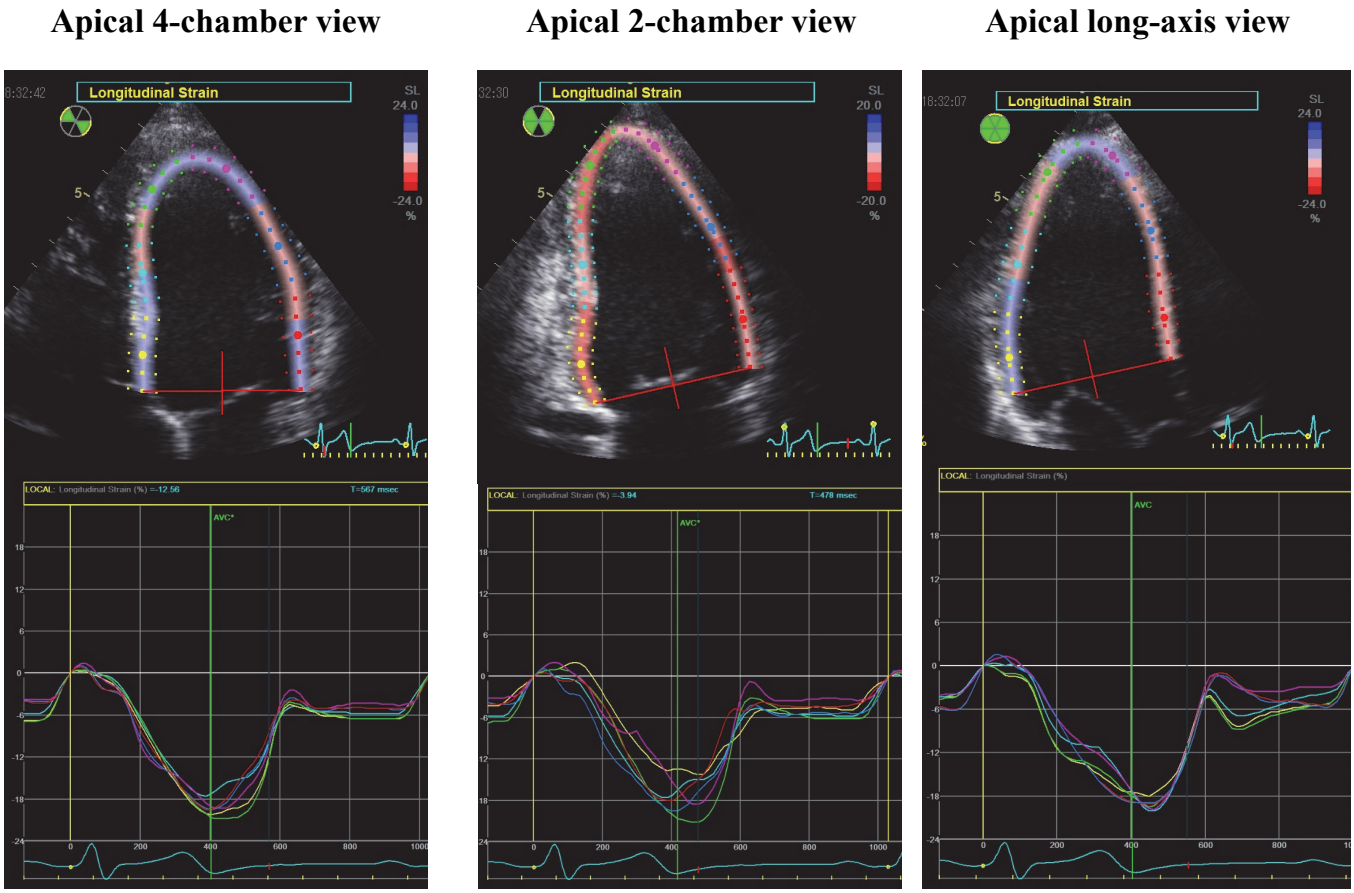

Fig. 2. Example of the assessment of LV longitudinal systolic myocardial function, known as GLS, by means of two-dimensional speckle-tracking imaging, showing color-coded speckle-tracking images and corresponding longitudinal time-strain curves. GLS is determined as the averaged peak longitudinal strain of 18 segments from the three standard apical views, and is expressed as an absolute value.

Utility of the Assessment of LV Longitudinal Myocardial Systolic Dysfunction for the Management of Stage A HF

Recent studies suggest that GLS might be helpful for the prediction of cardiovascular outcomes even for a general population[6, 12, 13]. The echocardiographic substudy from the Copenhagen City Heart Study used 1,296 participants from a general population who underwent a health examination, including conventional echocardiography and GLS measurement[6]. During a median follow-up of 11 years, lower GLS was associated with a higher risk of the composite end point of incident HF, acute myocardial infarction, or cardiovascular death, and an association that persisted after multivariable adjustment for age, gender, heart rate, hypertension, systolic blood pressure, LVEF, LV mass index, LV dimension, deceleration time, left atrium dimension, E/e', and pro B-type natriuretic peptide. In addition, GLS provided incremental prognostic information beyond the Framingham Risk Score, the Systemic Coronary Evaluation risk chart, and the modified ACCF/AHA Pooled Cohort Equation for the composite outcome and incident HF. LV longitudinal myocardial systolic dysfunction as assessed in terms of low GLS is altered in Stage A HF patients and can be an early marker of LV dysfunction, and, therefore, may point to cardiovascular morbidity and mortality. The next section will deal in more detail with the utility of LV longitudinal myocardial systolic dysfunction for individual comorbidity in Stage A HF patients.

1. LV Longitudinal Myocardial Systolic Dysfunction and Hypertension

With a proven population attributable risk of 39% for men and 59% for women, hypertension is the most common risk factor for HF[14]. Moreover, men with hypertension have a higher lifetime risk of developing HF than normotensive men[15]. Over 30% of Stage A HF patients during the surveyed period had blood pres-

sure above the target blood pressure, despite being diagnosed with hypertension[16]. Previous studies have reported a prevalence of low GLS values, ranging from 15% to 42%, for patients with hypertension, depending on the severity and control of hypertension[17-20]. Bendiab *et al*. found that 46% of patients showed low GLS values (<17%), and low GLS was associated with long-lasting hypertension and uncontrolled blood pressure for 200 outpatients with hypertension with preserved LVEF without overt HF. Moreover, Chen *et al*. reported that patients with uncontrolled blood pressure (≥140/90mmHg) were associated with low GLS regardless of LV hypertrophy for 276 patients with treated hypertension[20].

2. LV Longitudinal Myocardial Systolic Dysfunction and DM

DM is another well-known risk factor for HF, and as important a comorbid disease of Stage A HF as hypertension. Lack of DM control is an important predictor of the new onset of HF, with every 1% increase in HbA1c correlating to an 8%−19% increase in HF incidence[21, 22]. The presence of LV longitudinal myocardial systolic dysfunction has been identified in DM patients with preserved LVEF without overt coronary artery disease or HF[23-32]. Nakai *et al*. reported that GLS in DM patients was significantly lower than that in age-matched normal subjects in spite of similar LVEF, and that 43% of DM patients showed LV longitudinal myocardial systolic dysfunction defined as GLS <17.2%[23], while Ernande *et al*. showed that 23% of DM patients with preserved LVEF had LV longitudinal myocardial systolic dysfunction defined as GLS <18%[26]. In addition, Holland *et al*. investigated the association of subclinical LV dysfunction as detected by GLS with long-term, 10-year outcomes in 230 asymptomatic patients with type 2 DM and preserved LVEF[33]. They found that patients with GLS <18.9% had significantly worse outcome than those with a higher percentage, and concluded that GLS was independently associated with the primary endpoint.

DM is also a major cause of HF with preserved LVEF (HFpEF) as well as hypertension, with HFpEF usually presenting as LV diastolic dysfunction. Some investigators have maintained that LV longitudinal myocardial systolic dysfunction, rather than LV diastolic dysfunction, should be considered the first marker of a preclinical form of DM-related cardiac dysfunction in DM patients with preserved LVEF without overt HF[27, 34]. Ernande *et al*. showed that LV longitudinal myocardial systolic dysfunction detected as GLS <18% was present even in DM patients with preserved LVEF and normal LV diastolic function[27]. Thus, it has been suggested that the progression of uncontrolled DM leads to LV myocardial systolic dysfunction as well as LV diastolic dysfunction, that GLS is associated with LV diastolic function, and that reduced GLS can coexist with LV diastolic dysfunction in DM patients with preserved LVEF, leading to HFpEF.

3. LV Longitudinal Myocardial Systolic Dysfunction and Obesity

Healthy lifestyle habits, including the maintenance of normal body weight at body mass index (BMI) <25 kg/m^2, are associated with lower lifetime risk of HF[15]. Compared to those with normal BMI, obese subjects were found to have twice the risk of developing HF, with a graded relationship between BMI and HF incidence, including for those in the overweight category[35]. Ho *et al*. observed that higher BMI was associated with low GLS in 6,231 participants[36]. They showed that higher circulating leptin concentrations were associated with low GLS, suggesting potential involvement of circulating adipokines in obesity-related LV damage. Suto *et al*. recently reported that GLS of overweight patients (BMI ≥25 kg/m^2) was significantly lower than that of non-overweight patients, and multiple regression analysis revealed that BMI was the independent determinant parameter for GLS as well as LV mass index in 145 asymptomatic type 2 DM patients with preserved LVEF without coronary artery disease[37]. Furthermore, Leung *et al*. have detected an association of weight loss with an increase in GLS in obese patients. They showed that in eight obese patients with type 2 DM with BMI of 44 ± 9 kg/m^2 who underwent sleeve gastrectomy, GLS improved from 13.2 ± 3.7% to 19.7 ± 2.2% after surgery[38].

4. LV Longitudinal Myocardial Systolic Dysfunction and Hypercholesterolemia

Hypercholesterolemia has become well known as an extremely strong risk factor for coronary artery disease; however, its direct effect on LV myocardial function remains unclear. Liu *et al*. used 28 experimental rabbit models to investigate the effect of hypercholesterolemia on LV myocardial function in an attempt to elucidate such an effect[39]. They showed that GLS in an atherogenic diet group was significantly lower than that in a normal chow group even though the two groups had similar blood pressure, heart rate, and LVEF. Furthermore, a significant inverse correlation was observed between GLS and low-density lipoprotein cholesterol (LDL-C). In addition, Di Salvo *et al*. showed that GLS in 45 children with heterozygous familial hypercholesterolemia was significantly lower than that in 45 age-, gender-, and LVEF-matched control healthy children, and a significant linear correlation was observed between LDL-C and GLS[40]. Since arterioscle-

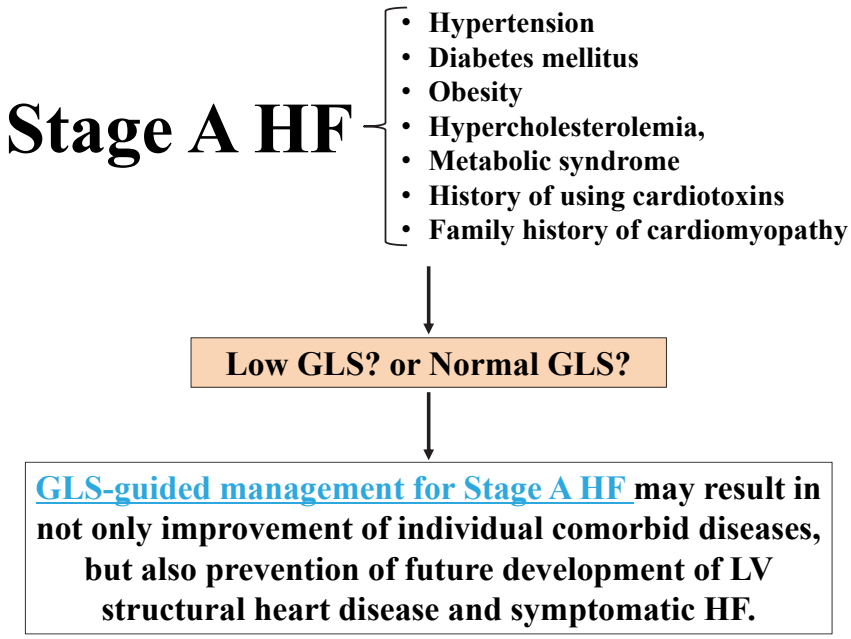

Fig. 3. Schema of the potential future perspectives or using global longitudinal strain for the management of Stage A HF.

rotic disease due to hypercholesterolemia can lead to an increase risk for HF, early intervention for hypercholesterolemia would be necessary to prevent eventual progression to overt HF.

5. LV Longitudinal Myocardial Systolic Dysfunction and Patients with History of Cardiotoxin Use

Patients without HF symptoms or LV structural abnormalities, but with a history of using cardiotoxins such as doxorubicin and trastuzumab, are included in Stage A HF. These cardiotoxins are used as anticancer drugs in chemotherapy treatment and have resulted in a recent decrease in the mortality rate for patients with various types of cancer. However, cancer therapeutics-related cardiac dysfunction (CTRCD) has become a leading cause of morbidity and mortality for cancer survivors[41, 42], and the mortality rate for patients with CTRCD is reportedly as high as 60% by 2 years after treatment[43]. This is caused by the irreversible LV myocardial changes due to anticancer drugs, such as myocyte loss, interstitial fibrosis leading to diminished LV contractility, reduced LV wall thickness, and progressive LV dilation. Anthracycline is an effective antineoplastic agent used for a wide spectrum of hematologic malignancies and solid tumors; however, the most serious adverse effect of anthracycline chemotherapy is progressive dose-dependent LV dysfunction followed by congestive HF, even years after the treatment has been completed. For this reason, there has been a growing interest in early detection of CTRCD by means of GLS, because it is a more sensitive and robust parameter for detecting subclinical LV myocardial dysfunction than other conventional LV functional parameters such as LVEF[44-47]. A systematic review of 1,504 patients during or after cancer chemotherapy showed that early changes in GLS appear to be the best measure for predicting cardiotoxicity[46]. Specifically, a drop in LVEF or occurrence of HF, reflected in a 10% to 15% early reduction in GLS during chemotherapy, appears to be the most useful parameter for the prediction of cardiotoxicity.

Future Perspectives for the Assessment of GLS for the Management of Stage A HF

The current ACCF/AHA guidelines recommend counseling, risk factor reduction, and control of concurrent diseases for Stage A HF[1-3]. Although the identification of individuals with Stage A HF is potentially useful for the implementation of HF-prevention strategies, not all Stage A HF patients develop LV structural heart disease or symptomatic HF, which can lead to advanced HF stages. This review article indicates that LV longitudinal myocardial systolic dysfunction as assessed in terms of low GLS can first appear in Stage A HF, which suggests the importance of the assessment of GLS for detecting subclinical LV dysfunction in this sub-clinical stage. Thus, GLS-guided management such as strict control of hypertension, DM, hypercholesterolemia and obesity may result in not only the

improvement of individual comorbid diseases, but also the prevention of future development of LV structural heart disease and symptomatic HF. However, more research is needed to further understand the efficacy of GLS-guided therapy using cardioprotective drugs such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, and mineralocorticoid receptor antagonists for Stage A HF patients. Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of diabetic medications currently indicated only for the treatment of type 2 DM. In addition to reducing glycated hemoglobin levels in patients with type 2 DM, SGLT2 inhibitors are associated with weight loss and reductions in blood pressure which are important comorbid diseases for Stage A HF[48-50]. Thus, SGLT2 inhibitors may have potential for a new therapeutic strategy for Stage A HF[51].

The Measurement of GLS has certain limitations, however; among known sources of variety, the primary determinant is post-processing. The most important limitation is that different vendors have reported significantly different measurements of GLS[52, 53]. However, this issue has been minimized since Strain Standardization Taskforce intervention[54]. Furthermore, the difference among vendors in GLS measurements is at most equivalent to or even smaller than that in LVEF measurements[53], and the reproducibility of GLS measurements was found to be as good as, and in many cases superior to that of conventional echocardiographic measurements[53].

Conclusion

HF is a worldwide healthcare epidemic, known as "The HF Pandemic." HF is likely to be more serious in the near future with the epidemiological transition and the accompanying aging of the population. In addition, there is a high prevalence of patients with Stage A HF, many of whom are not being appropriately or adequately treated for their risk factors. Thus, GLS-guided management for patients with Stage A HF may have the potential of preventing progression to later stage HF (**Fig. 3**).

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