Review Article

Heart Failure with Improved Ejection Fraction

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Abstract

Cardiac remodeling is generally an adverse sign linked to the progression of heart failure (HF). However, in remodeled hearts, reverse remodeling is an important sign of cardiac recovery associated with a better prognosis. Ejection fraction may improve spontaneously following resolution of the processes that promote cardiac dilatation. In HF with reduced ejection fraction, treatment with neurohormonal blockade is an important strategy to promote improvements in ejection fraction. Improved ejection fraction can identify recovered patients with a better prognosis. In patients with HF with reduced or mildly reduced ejection fraction undergoing treatment, we should always investigate the ejection fraction development and optimize treatment by targeting an improved ejection fraction.

HF with improved ejection fraction is a current topic with several new publications, and given its importance, it has been highlighted in the main HF guidelines.

Update of the guidelines for the diagnosis and treatment of HF

In view of a better outcome for patients with improved ejection fraction, the European and Brazilian HF Societies have updated concepts and underscored the value of reverse remodeling. Therefore, in 2021, the guidelines presented a revised patient classification based on ejection fraction and provided better defined groups (without an overlap of ejection fractions), classifying patients into 4 groups that further highlight and better define improved fraction ejection (Table 1).[1-3]

Valuing improved ejection fraction was important as it is a clinical finding that can identify patients with a better prognosis. It should be systematically investigated in patients with reduced or mildly reduced ejection fraction, as the improvement in ejection fraction indicates better control of HF and myocardial injury, whereas the lack of improvement with treatment may indicate more severe disease, although it more often indicates that treatment could be implemented.

Ventricular remodeling

Ventricular remodeling is the process by which ventricular size, shape, and function are regulated by mechanical, neurohormonal, and genetic factors.[4] Remodeling may be physiological and adaptive during normal growth or pathological due to myocardial infarction, cardiomyopathy, hypertension, or valvular disease. Myocardial remodeling can be defined as molecular, cellular, and interstitial changes in the myocardium leading to changes in the size, mass, geometry, and function of the heart as a result of myocardial injury.[4] In response to these changes, there is cardiac function reduction and cardiac dilatation associated with circulatory congestion, which characterize HF as a clinical syndrome.[4] Cardiac remodeling is generally an adverse sign linked to HF progression. However, in remodeled hearts, reverse remodeling is an important sign of cardiac recovery associated with a better prognosis.

The pathophysiological importance of cardiac remodeling has been well demonstrated in the studies conducted by the Pfeffers. Initially, Marc and Janice Pfeffer, in experimental studies using a rat model of myocardial infarction, showed that the death of rats was strongly associated with the degree of cardiac dilatation and reduction of ejection fraction.[5,6] The demonstration of the pathophysiological and prognostic importance of cardiac remodeling in HF was expanded with the results of studies using angiotensin-converting enzyme (ACE) inhibitors in the treatment of these infarcted rats, which showed that ACE inhibitors prevented cardiac remodeling and, in some cases, promoted reverse remodeling.[6] The rats treated with ACE inhibitors that showed attenuated ventricular dilatation or reverse remodeling had better outcomes than those that did not.[5,6]

Subsequently, Marc Pfeffer coordinated the Survival and Ventricular Enlargement (SAVE) trial, whose results showed that this remodeling concept could also be applied to humans and that treatment with ACE inhibitors modified the natural history of myocardial infarction and infarction-related HF.[7] Patients with myocardial infarction and ejection fraction of < 40% treated with captopril had a reduction in cardiovascular events of approximately 40%.[7]

Since then, the role of cardiac remodeling has been investigated in HF studies and in HF registries, confirming these findings.[8-17]

Keywords

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Table 1 – HF classification according to ejection fraction[1-3]

Heart failure reduced ejection fraction (HFrEF) – EF < 40%
Heart failure mildly reduced ejection fraction (HFmrEF) – EF 41%-49%
Heart failure preserved ejection fraction (HFpEF) – EF > 50%
Heart failure improved or recovered ejection fraction (HFimpEF). For those with an EF of < 40% who had a 10-point increase and remained with an EF of > 40%.

Reverse ventricular remodeling

Cardiac dilatation is therefore identified as an important and definite marker of poor prognosis. Conversely, its reversal is associated with improved outcomes.

Spontaneous reversal occurs in situations in which the cause of ventricular dysfunction has been corrected, such as in heart rate control in tachycardiomyopathy, in cases of treated hypothyroidism and hyperthyroidism, in hypertensive patients after hypertension control has been achieved, in myocarditis that has reversed the inflammatory condition, and when a cardiotoxic agent is discontinued, such as cessation of drinking in cases of alcoholism or of a prescribed chemotherapeutic agent.[12]

Reverse remodeling also occurs as a result of the treatment of ventricular dysfunction, and several studies have shown that drugs or procedures that modify ventricular remodeling, either by preventing or delaying cardiac dilatation or by improving ejection fraction, are associated with better patient outcomes.[17,18] Not all drugs used in the treatment of HF influence cardiac remodeling.[18] Post-infarction animal studies showed that beta-blockers, aldosterone antagonists, and renin-angiotensin system (RAS) inhibitors prevented cardiac dilatation, whereas hydralazine and digitalis did not.[18]

Therefore, clinical and experimental evidence suggests that the renin-angiotensin-aldosterone system and the sympathetic system play an important role in the process. Sacubitril/valsartan and, to a lesser extent, sodium-glucose cotransporter 2 (SGLT2) inhibitors also promote reverse remodeling, and this reversal plays a role in improving the prognosis of patients treated with these drugs.[19-21]

The Valsartan Heart Failure Trial (Val-HeFT) also confirmed the association between reverse remodeling and improved prognosis, but it went further and documented the importance of the magnitude of reversal in remodeling. In the Val-HeFT, where patients were divided into quartiles according to the magnitude of remodeling, treatment with angiotensin-receptor blocker proved to be effective in reducing mortality from quartiles 2 to 4 by promoting a reduction of 11%, 15%, and 20% in the risk of death in quartiles 2, 3, and 4, respectively.[18] The Vasodilator-Heart Failure Trial (V-HeFT) I and V-HeFT II also observed the role of the magnitude of reversal in remodeling and reported that a 5-point increase in ejection fraction was the strongest predictor of mortality among the study variables.[22] About 30% of patients had a > 5-point increase in ejection fraction and 50% had a > 10-point increase in ejection fraction.

The percentage of patients who show improved ejection fraction when treated is still a matter of debate. Reversal of cardiac dilatation has been described in 30% to 60% of patients treated with neurohormonal blockade. Cioffi et al, evaluating factors associated with improved ejection fraction in patients over 70 years of age, found improved ejection fraction in 36% of outpatients during a mean follow-up of 17 months. Predictors of this improvement included absence of diabetes, history of hypertension, and treatment with beta-blockers, the latter increasing by 3.4 times the chance of reversal.[23] Overall, studies have shown that patients with coronary artery disease experience less reverse remodeling, especially those with myocardial infarction, which has generally been observed in patients with complete left bundle branch block.

Improvement in cardiac remodeling has also been observed in registries of HF cases. In the IMPROVE-HF Registry, which analyzed 3994 patients hospitalized for compensated HF, ejection fraction improved by more than 10% in 28.6% of patients.[8]

In the Swedish HF Registry, analyzing 4942 cases, patients with improved ejection fraction had a lower risk of mortality than those without any improvement.[9] The worse outcome was observed in those with reduced ejection fraction[9] (Figure 1). This registry showed that the lowest mortality occurred in patients with mildly reduced or reduced ejection fraction who had some increase in ejection fraction; increases in ejection fraction were observed in 25% of patients with mildly reduced ejection fraction and in 26% with reduced ejection fraction, of whom 10% achieved an ejection fraction of > 50% and 16% remained at mildly reduced ejection fraction levels[9] (Figure 1). The data from the registry and previously mentioned data underscore the importance of improved ejection fraction, which promotes an improvement in prognosis even when not achieving the levels proposed as improved ejection fraction in current guidelines.

When analyzing cardiac remodeling, increased adrenergic activity appears to play a major role in ventricular remodeling, since beta-blockers have shown greater reversal of cardiac dilatation than ACE inhibitors (Figure 2). While ACE inhibitors attenuate ventricular dilatation and slightly increase ejection fraction, beta-blockers are associated with a marked reduction in ventricular diameters and improvements in ejection fraction.[24]

There is a growing number of studies documenting the importance of reverse ventricular remodeling in

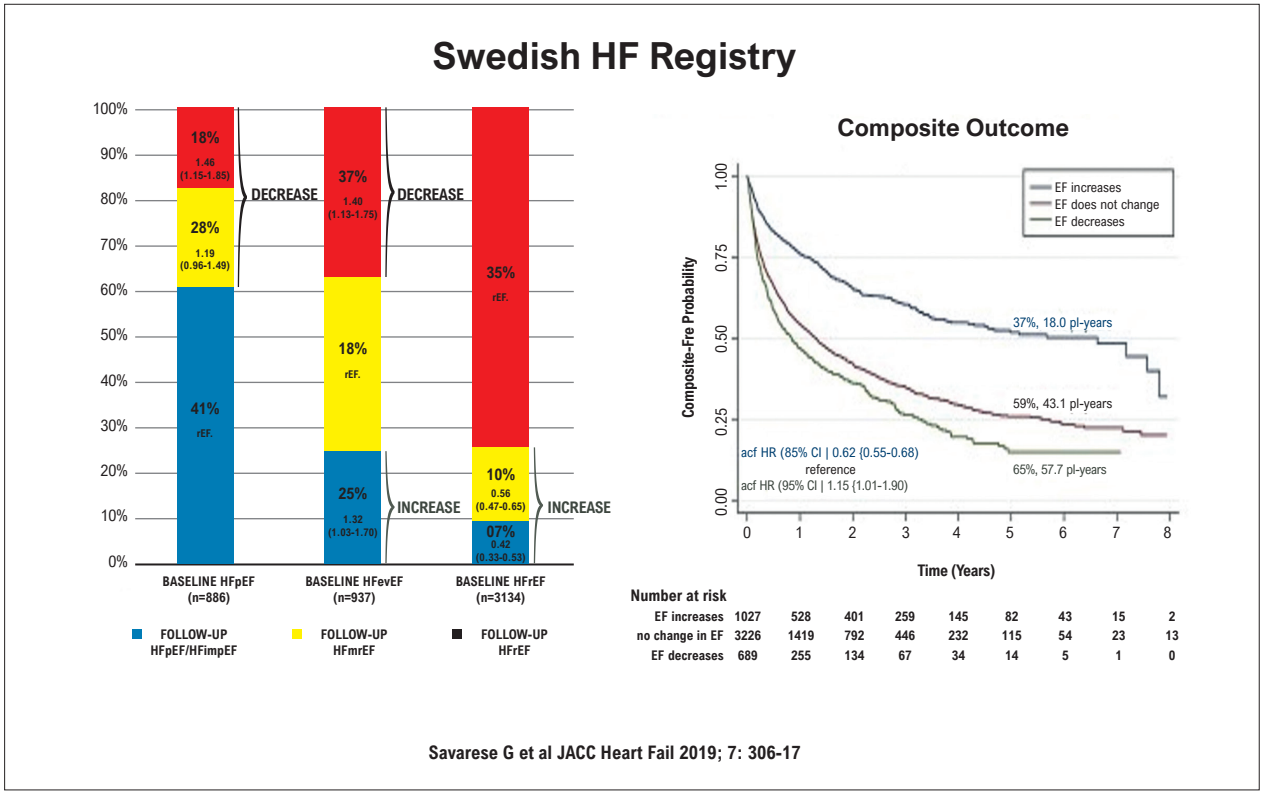

Figure 1 – *Reverse cardiac remodeling with improved ejection fraction was accompanied by a significant reduction in mortality. HFpEF: heart failure preserved ejection fraction; HFrEF: heart failure reduced ejection fraction; HFimpEF: heart failure improved or recovered ejection fraction; HFmrEF: heart failure mildly reduced ejection fraction.*

the prognosis of HF.[10-22] Patients who show regression of ventricular dilatation or improvement in ejection fraction with treatment have a better quality of life and lower morbidity/mortality than those with continued dilatation.[10-22]

In the study by Cioffi et al, follow-up results showed that patients with reverse remodeling had lower mortality (3%) than those without reverse remodeling (22%).[23] In the V-HeFT I and II, mortality at 1-year follow-up was 29%, 16%, and 6%, respectively, for patients with a > 6-point reduction in ejection fraction, those with values between -5 and +5, and those with a > 5-point increase in ejection fraction.[22]

Hoshikawa et al found an association of prognosis with reverse cardiac remodeling.[25] They divided patients into 3 groups: those with complete reverse remodeling, defined as left ventricular (LV) end-diastolic diameter < 55 mm and fractional shortening > 25%; those with partial reversal; and those without reversal. All patients without reversal of cardiac dilatation died within a mean follow-up of 5 years. All patients who had some reversal of cardiac dilatation survived. In this study, in which all patients were treated with neurohormonal blockade, 78% had reversal of cardiac dilatation, 57% of whom had complete reverse remodeling.

The same research group reanalyzed their patients, and Matsumura et al, evaluating the role of reverse remodeling in long-term outcomes, found that all patients with regression of cardiac dilatation survived, whereas those with increased cardiac dilatation either died or required a transplant at 12-year follow-up.[26] In this population of patients with dilated cardiomyopathy, 35.6% had some reversal of cardiac dilatation, 37% of whom had normalization of diameters and ejection fraction.[26] Overall, the authors reported that all patients who showed some reversal remained alive at the end of 12 years, indicating that even small improvements are indicative of a good response to treatment.[26]

In addition to clinical trials and small-sample studies, reverse cardiac remodeling was also the topic of a meta-analysis involving 69,766 patients from 30 randomized trials, which reported a strong association between improved ejection fraction and reduced mortality.[27] Overall, there was a significant 49% reduction in mortality in patients who had improved ejection fraction compared with those who did not.[27] Regression analysis showed that a 5% improvement in mean ejection fraction corresponded to a 14% relative reduction in mortality (odds ratio 0.86; 95% CI, 0.77-0.96; p=0.013). Overall, patients with reverse remodeling were 4.9 times more likely to survive than those without reverse remodeling, for each 5% absolute increase in ejection fraction.[27]

A much better outcome is observed in patients with reversal of cardiac dysfunction, even if only partial, so that we should consider it one of the primary goals of treatment. Patients without reversal of cardiac dysfunction should have their treatment regimen reassessed and, in the absence of reversal, be followed up more closely and carefully, as these are the patients

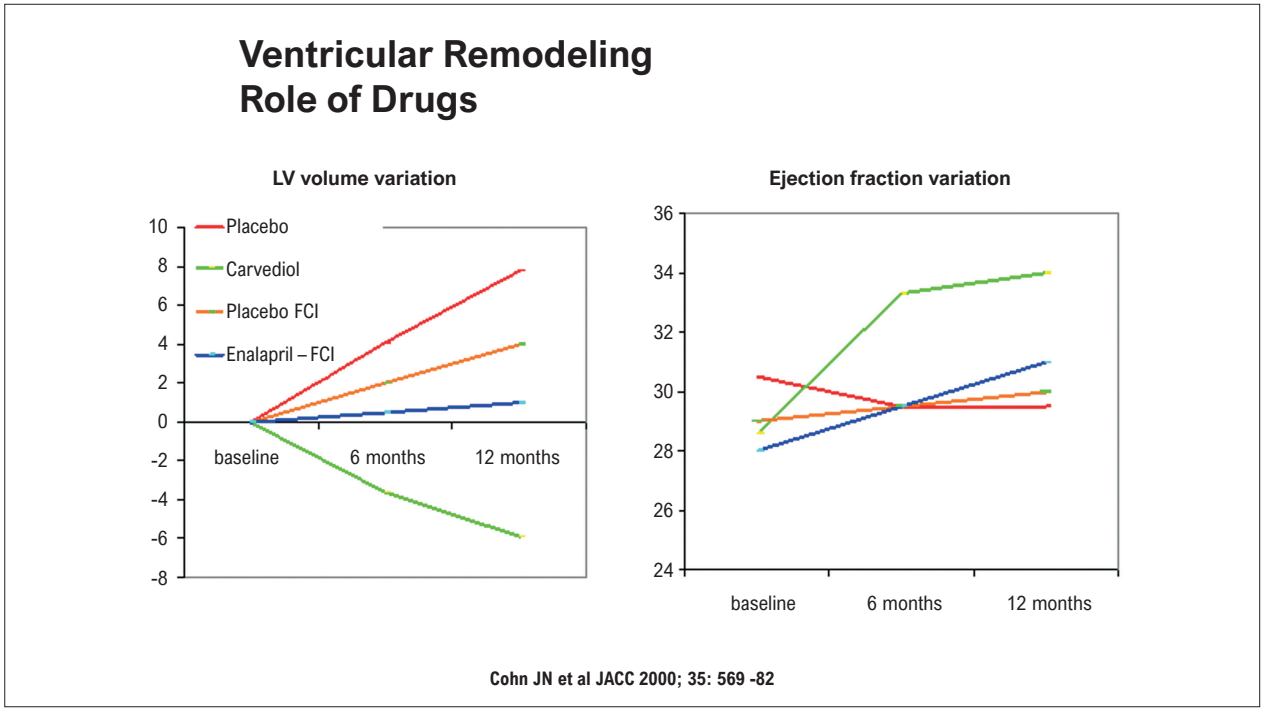

Figure 2 – *Role of drugs in reverse ventricular remodeling. Beta-blockers were more effective in reversing cardiac remodeling. LV: left ventricular; FCI: Function Class I.*

at risk of complicated outcomes. An effective treatment should lead to reverse cardiac remodeling. It is worth mentioning that reversal is more frequent when drugs that have been proven to modify the evolution of patients with HF are used, a blocker of the renin-angiotensin system, a beta-blocker, spironolactone and an inhibitor of SLGT2, which has been called the four fantastic., as they reduce mortality, hospitalizations, and procedures such as cardiac resynchronization, also promote reverse remodeling.[12-22] No reversal may indicate that the prescribed doses are insufficient or the disease is so severe that the patient will not respond as desired to the proposed regimen.

In the treatment of HF, the prescribed dose is extremely important. Reverse remodeling is often not observed because the drugs have been prescribed at low doses. The importance of the prescribed dose was highlighted in the FAST-Carvedilol study conducted at our institution.[28] In this study, half of the patients were discharged with a carvedilol dose of 3.125 mg or 6.25 mg twice daily and the other half had their dose increased rapidly during hospitalization and were discharged with the maximum tolerated dose. In the outpatient clinic, the carvedilol dose was not increased by their physicians for various reasons, mostly for borderline blood pressure, so that the mean dose of carvedilol was 6.99 mg/day in the control group and 16.19 mg/day in the intervention group. During follow-up, the intervention group showed reversal of cardiac dilatation, which was observed in the first 3 months of treatment (Figure 3), whereas the low-dose group showed no reversal.[28] The 1-year survival was 43.5% in the control group vs 65.2% in the intervention group. Our data draw attention to the critical role of dose in both reversing cardiac dilatation and reducing mortality (which are probably interconnected).[28]

More accurate drug titration has been implemented in specialized HF clinics. In a study conducted in the Netherlands, in which treatment optimization was led by nurses, a higher rate of patients achieved the effective doses (target doses) after nurse-led up-titration.[15] Of 345 patients with HF with reduced ejection fraction at 9-month follow-up, 69% achieved ≥ 50% of the recommended dose of RAS inhibitors and 73% achieved ≥ 50% of the recommended dose of beta-blockers. The main reasons for not achieving the target doses were hypotension (RAS inhibitors and beta-blockers), bradycardia (beta-blockers), and renal dysfunction (mineralocorticoid receptor antagonists).[15] LV ejection fraction improved from a mean of 27.6% at baseline to 38.8% at 9-month follow-up. Each 5% increase in LV ejection fraction was associated with a reduction in mortality of 16% (hazard ratio 0.84 [0.75–0.94], p=0.002) and 15% (hazard ratio 0.85 [0.78–0.94], p=0.001) for the composite endpoint of death and/or hospitalization after a mean of 3.3 years of follow-up. The authors concluded that optimized up-titration in a specialized nurse-led HF clinic promoted an improvement in LV ejection fraction and a reduction in morbidity/mortality in patients with new-onset HF.[15]

We have used this approach of assessing ejection fraction improvement as a guide to treatment. In patients who do not experience reverse remodeling, we have increased the dose of medication, especially of beta-blockers, thus achieving reversal of cardiac dilatation, which had not been achieved with the usual dose. In patients who have a persistent heart rate of > 70 bpm with optimal treatment, the use of ivabradine has been effective in reversing cardiac dilatation.[24]

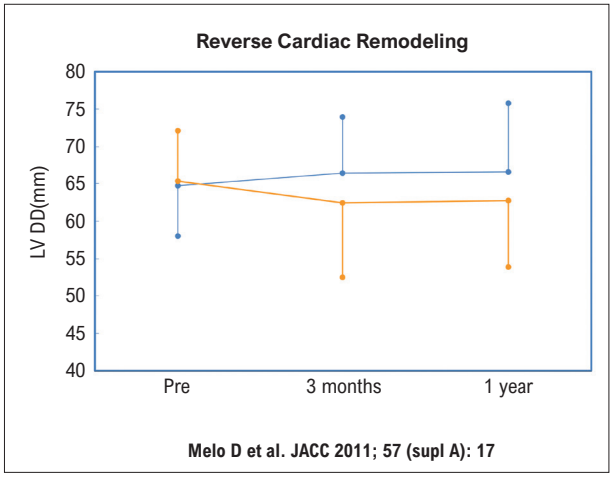

Figure 3 – *The importance of carvedilol dose in reverse ventricular remodeling. Patients receiving a dose of 3.125 mg or 6.25 mg twice daily showed no reduction in ventricular diameters (blue line), but this reduction was observed in those receiving a dose of 12.5 mg or 25 mg twice daily (orange line).*

At the University of São Paulo Heart Institute-InCor, we have attempted to determine the role of improved ejection fraction in HF prognosis by investigating patients from the different teams of InCor, Brazilian Unified Health System (SUS), health plans, private patients, patients with cardiomyopathy, valvular disease, or coronary artery disease, and geriatric patients.[24] We investigated all patients who were treated at InCor in 2017 with a diagnosis of HF (13,121 patients). Of these, 3670 had reduced ejection fraction and two follow-up echocardiograms. In this group with two echocardiograms, 64.5% showed some improvement in ejection fraction, and in 31.3% this improvement allowed us to classify them in the improved ejection fraction group according to the new guidelines; 30% showed no improvement in ejection fraction. At 1000-day follow-up, mortality was 16.3% for patients with improved ejection fraction vs 30.3% for those with no improvement in ejection fraction. Any improvement in ejection fraction was associated with a mortality rate lower than that observed in patients with no improvement (22.4% vs 30.3%), supporting evidence that any reversal of cardiac remodeling is associated with an improvement in the prognosis of patients with HF.[24]

A crucial point to consider in the presence of improved ejection fraction is that, in most cases, the patient is not cured. The patient experiences reverse remodeling and shows improved ejection fraction due to adequate response to treatment, but treatment withdrawal or even dose reduction, in general, can promote cardiac re-remodeling with reduced ejection fraction. This reduction was well documented in the TRED-HF trial, designed to monitor ejection fraction after treatment withdrawal, reporting a relapse of the dilated cardiomyopathy in approximately 40% of cases.[29] After reinstating treatment, not all patients returned to their pre-withdrawal ejection fraction levels. Therefore, the take-home message is that the treatment should not be withdrawn because the patient has improved ejection fraction.

In conclusion, we should always optimize the treatment of HF by prescribing drugs at the doses recommended in Guidelines and in clinical trials.[1-3] To confirm the effectiveness of treatment, an echocardiogram can be obtained to determine whether the treatment has promoted an improvement in ejection fraction. If an improvement has been achieved, the treatment can be considered effective and there is no need to review the doses or the treatment regimen.[12-22] If no reversal of cardiac dilatation has been documented, this finding is indicative of treatment ineffectiveness and treatment should therefore be improved by up-titrating drug doses, by prescribing new drugs, or even by recommending an intervention.[1,2]

Patients with improved ejection fraction have a better prognosis, better quality of life, and lower morbidity/mortality than those with an ejection fraction that does not improve or that deteriorates after treatment.

Author Contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Barretto ACP.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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This article does not contain any studies with human participants or animals performed

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