Frailty, Exercise and Nutrition

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KEYWORDS

• Frailty • Sarcopenia • Physical exercise • Nutrition • Multicomponent intervention

KEY POINTS

- Age, genetics, epigenetics (nutrition, physical exercise), and environment play key roles in the frailty process.
- Frailty may be delayed or even reversed by physical exercise, with or without nutrition supplementation, or by targeted interventions on specific frailty components.
- A review of physical activities and nutrition interventions testified that sarcopenia, a major component of physical frailty, could be delayed or reversed.
- Multidomain interventions are promising. First results are encouraging, but the sole economic evaluation performed to date demonstrated the very high costs of such interventions.

Frailty is characterized by increased vulnerability to stressors that puts older subjects at risk of developing adverse outcomes, including hospitalization, disability, and mortality.[1,2] With population aging, frailty is becoming a silent epidemic, affecting older adults.[3] In the largest survey to date performed in Europe, namely the Survey of Health, Aging and Retirement in Europe (SHARE), a multidisciplinary, cross-national panel database of microdata on health, socioeconomic state, and social and family networks including more than 85,000 individuals aged 65 or over (approximately 150,000 interviews) from 19 countries across Europe and Israel,[4] the prevalence of frailty (using an adapted version of Fried's criteria of physical frailty[5]) reached 17%, varying from 5.8% in Switzerland to 27.3% in Spain. The prevalence of prefrailty was considerably higher, ranging from 34.6% in Germany to 50.9% in Spain.[6] In SHARE, mortality exponentially increased from robust to prefrail to frail subjects (**Fig. 1**).[7]

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Clin Geriatr Med 31 (2015) 375–387
http://dx.doi.org/10.1016/j.cger.2015.04.006 geriatric.theclinics.com

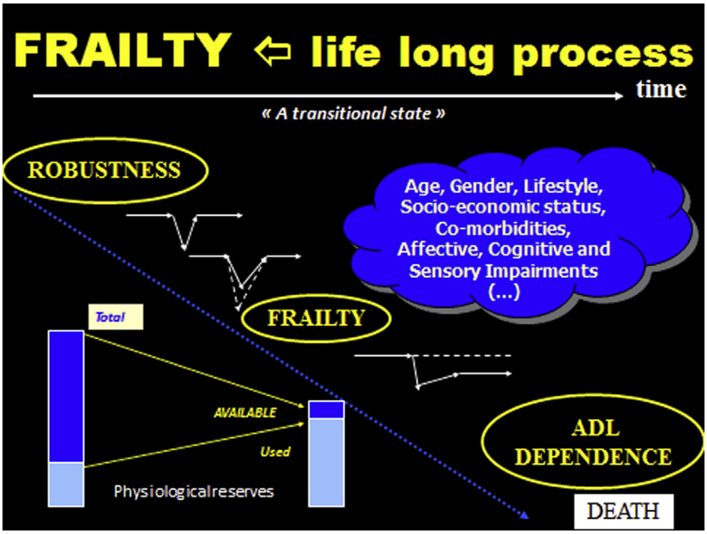

Fig. 1. Frailty is included in a transitional state between robustness, dependency, and death. ADL, activities of daily living.

Such data explain the urgent need to establish a universal definition of the frailty syndrome,[3] to detect prefrail individuals at an early stage in the community, and to implement effective prevention strategies.[8–10] Early intervention in frail individuals has the potential to retard or prevent disability, one of the key objectives of gerontology today.

The main components of the frailty phenotype as described by Fried and colleagues[5] are physical. Age, undernutrition, and sarcopenia play major roles in the vicious cycle of frailty,[11–13] explaining why various authors have proposed sarcopenia to be considered as the equivalent of physical frailty.[14–16] After the publication of the European consensus definition of sarcopenia,[17] a systematic review by an international working group of all published randomized trials (RCTs) showed that sarcopenia could be reversed, either by physical exercise, protein/amino acid diet interventions, or a combination thereof.[15] However, there again, the main problem with sarcopenia is its early detection, based on acknowledged criteria that need to be adapted to differences in the studied populations.[18–21]

In this rapidly evolving context, a major issue is linked to the fact that no consensus yet exists on how to identify prefrail and frail adults within the community, as recently stressed by the new British Geriatric Society guidelines.[22] The main purpose of the present article is to demonstrate that physical frailty, closely resembling sarcopenia, may be reversed by physical exercise, nutritional interventions, or a combination of the two. It should also be borne in mind that, beyond the physical features, the frailty syndrome also includes at least two other components, namely cognition and socioeconomic status.[23–25] Physical and cognitive frailty share some common pathogenetic pathways,[26] and consequently, certain interventions might impact both conditions.

This article first reports the spontaneous course of frailty conditions, and then focuses on randomized, controlled frailty interventions (such as physical exercise, nutrition, combined exercise plus nutrition, and multifactorial interventions) or metaanalysis in community-dwelling older adults or volunteers published in 2012, 2013, and 2014. The main take-home messages that emerge from recent literature are summarized.

DYNAMICS OF FRAILTY

The SHARE study[6] started in 2004 with a first epidemiologic survey using criteria adapted from Fried and colleagues namely shrinking, exhaustion, low physical activity, muscle weakness, and slow gait speed. This research was followed by 3 further surveys (waves) performed in 2006, 2009, and 2011.[4] Transitions between the different frailty states were analyzed. Observations from the first wave (2004) to the second (2006) included a follow-up of 14,448 European adults aged over age 65. In 2004, 52.1% of the population were not frail, 39.1% prefrail, and 8.8% frail. Two years later, without any known or programmed intervention, 22.1% had worsened, 61.8% had not changed, and 16.6% had improved their status.[27] Interestingly, among those whose status worsened, more than two-thirds moved from nonfrail in 2004 to prefrail at the next wave.[27] Over the same period, frail subjects were at increased risk of mobility disorders, comorbidities, and an inability to perform basic and instrumental activities of daily living (ADL; $P<.001$ for all).[28]

Between the second (2006) and the fourth (2011) waves, naturally occurring transitions were observed for 15,776 European adults.[29] The results presented in Fig. 2

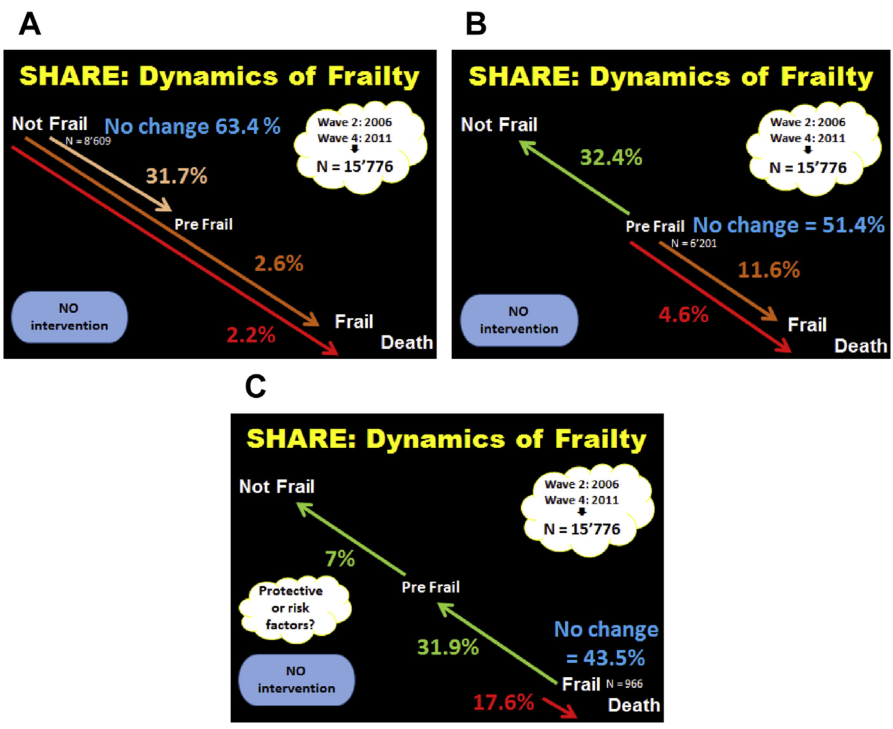

Fig. 2. (*A*) Natural transitions occurring from the not-frail state to other clinical conditions between the second (2006) and fourth (2011) waves of the SHARE study. (*B*) Natural transitions occurring from the prefrail state to other clinical conditions between the second (2006) and fourth (2011) waves of the SHARE study. (*C*) Natural transitions occurring from the frail state to other clinical conditions between the second (2006) and fourth (2011) waves of the SHARE study. (*Adapted from* Borrat-Besson C, Ryser VA, Wernli B. Transitions between frailty states – a European comparison. In: Börsch-Supan A, Brandt M, Litwin H, et al, editors. Active aging and solidarity between generations in Europe. Berlin: De Gruyter; 2013. p. 175–86.

confirm that the nonfrail or robust state deteriorates over time, as do the prefrail and frail states. Death is the unavoidable consequence of this temporal deterioration.

However, the most important and positive message to come out of these data is the reversibility of the prefrail state toward a robust state, observed in one-third of all individuals. A second optimistic message is that the frail state is also reversible in approximately one-third of the older adults studied, with transition toward the prefrail or even nonfrail state.

The Precipitating Events Project in the United States also confirmed that frailty among older persons is a dynamic process, characterized by frequent transitions between frailty states over time.[30] This study of 754 non–ADL-disabled community-living persons aged 70 years or older, using Fried's criteria, found that 57.6% of the participants had at least 1 transition between any 2 of the 3 frailty states over 54 months, with rates of 36.8%, 21.5%, and 9.2% for 1, 2, and 3 transitions, respectively. However, in this study, transitions to states of greater frailty were more common (rates of $\leq$43.3%) than transitions to states of lesser frailty (rates of $\leq$23.0%).

FACTORS ASSOCIATED WITH TRANSITIONS IN THE FRAILTY STATE

Two recent papers focused on identifying the factors that positively or negatively contribute to changing the frailty state. The most recent and informative study included 3018 community-dwelling Chinese adults aged over 65 years of age, whose frailty state was classified according to the Fried criteria on 2 visits performed 2 years apart.[31] At baseline, 850 (48.7%) men and 884 (52.6%) women were prefrail. Among these, 23.4% of men and 26.6% of women improved after 2 years, whereas 11.1% of men and 6.6% of women worsened.[31] Other important conclusions from this study were that there are important gender differences, namely:

- More men than women ($P<.001$) deteriorated into frailty
- Factors that accelerate the worsening or improvement of the functional state were different between genders.

Worsening of nonfrail adults was related to older age and previous cancer in men, while corresponding factors for women were older age, chronic obstructive pulmonary disease, previous stroke, or hospitalization. Moreover, worsening of the prefrail state was related to older age and previous hospitalization in men, and to osteoarthritis, previous stroke, or hospitalization in women.

On the other hand, improvement of the prefrail state was related to lower age, higher Mini Mental State Examination score, and absence of stroke in men, and to lower age, absence of diabetes, no previous hospitalization, and higher socioeconomic status in women. Improvements of the frail state were only observed in men, and were related to the absence of stroke.[31]

The information provided by this study is complemented by an observational report from the San Antonio Longitudinal Study of Aging on changes in frailty characteristics from 1992 through 1996 to 2000 through 2001 in a cohort of about 600 older Mexican Americans and European Americans (mean age of 70 years at inclusion).[32] In this study, the authors identified the following significant predictors of progression in any frailty characteristic:

- Diabetes with macrovascular complications (odds ratio [OR], 1.84; 95% CI, 1.02–3.33)
- Fewer years of education (OR, 0.96; 95% CI, 0.93–1.0).

Another important piece of information to come out of this study is that frail individuals were more likely to die than to remain frail. Indeed, death rates increased in line with poorer baseline frailty status, low performance-based measures, and low physical activity.[32] Taken together, this body of evidence indicates that frailty interventions could be important to facilitate frailty reversibility.[33,34]

In this article, only the results of randomized, controlled interventions in frail older adults published between 2012 and the end of 2014 are considered. Four types of interventions have been tested to date, namely physical exercise alone, nutritional supplements, a combination of physical exercise and nutrition, and multifactorial interventions.

PHYSICAL EXERCISE IN FRAIL ELDERS

Two metaanalyses of RCTs investigating the effects of exercise were published in 2012[35] and 2014.[36] The first metaanalysis included 8 RCTs, all published before 2010, and selected from among 146 trials.[35] The 8 trials investigated included 1068 frail participants selected according to predetermined Fried criteria (age range, 75.3–86.8 years) and randomly assigned to either the inactive control group or the exercise intervention group; that is, simple or comprehensive, lasting at least 60 minutes, twice a week with a follow-up of at least 8 months.[35] Frail individuals taking part in regular exercise showed improvements in several parameters, namely:

- Gait speed (evaluated in 4 trials, n = 459) increased by 0.07 m/s (95% CI, 0.02–0.11; P = .005)
- Berg Balance Scale score (fully evaluated in 3 trials, n = 356) improved by a weighted average of 1.69 (95% CI, 0.56–2.82)
- ADL performance improved; mean difference of 5.33 (95% CI, 1.01–9.64).

However, the exercise intervention had no significant effects on either the Timed Up & Go test (3 studies, n = 400) or quality of life (2 studies, n = 409 for the physical component and n = 187 for the mental health component).[35]

The second study, published in 2014, reports a systematic review and metaanalysis of 12 RCTs (published up to 2013), and compared multicomponent physical exercise programs with an inactive control group of community-dwelling older adults, defined as frail according to physical function and physical difficulties in ADL.[36] Again, physical exercise programs (at least 45 minutes twice a week with follow-up from 6 months to 2 years) had a positive impact on several variables, namely:

- Normal gait speed (mean improvement 0.07 m/s; [95% CI, 0.04–0.09])
- Fast gait speed (mean improvement 0.08 m/s; [95% CI, 0.02–0.14])
- Short physical performance battery scores (mean improvement, 2.18; [95% CI, 1.56–2.80]).

Conversely, results were inconclusive for endurance outcomes, and no consistent effect was observed either on balance or ADL functional mobility. Moreover, the evidence comparing different modalities of exercise was scarce and heterogeneous.[36]

Based on these recent data, it seems clear that physical exercise programs can delay or reverse the prefrailty or frailty states. It is important to mention that the RCTs included in the two metaanalyses are totally different, but still yielded similar positive results. However, the exercise programs and the length of follow-up varied considerably from 1 RCT to another, precluding any specific recommendations regarding the type, duration, or frequency of physical exercise.

The largest study on the impact of increased physical activity in older subjects is the Lifestyle Interventions and Independence for Elders (LIFE) trial,[37] which randomized subjects to a physical activity intervention versus successful aging education. This study recently published data on frailty obtained from 424 community-dwelling persons (mean age, 76.8 years) with a sedentary lifestyle and at risk of mobility disability.[38] The prevalence of frailty at 12 months was significantly lower in the intervention group (10%) compared with the control group (19.1%). The number of frailty criteria was also reduced in frail and multimorbid subjects.

NUTRITION IN FRAIL ELDERS

RCTs of nutritional interventions in frail individuals remain scarce, although the role of undernutrition in the frailty process is well-established.[11] Thus, the preventive impact of protein-energy supplementation in frail older adults remains to be proven.

One recent RCT on this indication included 87 frail community-based adults (usual gait speed <0.6 m/s; Mini Nutritional Assessment <24; mean age, 78 years) with low socioeconomic status.[39] The intervention group received two 200-mL cans of a liquid formula providing 400 kcal, 25 g protein, 9.4 g essential amino acids, and 400 mL water per day for 12 weeks, and its impact was compared with a control group who received no supplementation.[39]

- Overall physical functioning did not change in the control group but improved by 5.9% in the intervention group.
- The short physical performance battery score declined by 12.5% in the control group, but remained stable in the intervention group.
- Gait speed decreased in both groups, but to a greater extent in the control group (11.3%) compared with the nutrition intervention group (1.1%).
- The Timed Up and Go score decreased by 11.3% in the controls, whereas it increased by 7.2% in the nutrition group.
- There were no changes in either group in hand grip strength or 1-legged standing performance.[39]

A second RCT assessed the impact of 24 weeks of dietary protein supplementation on muscle mass, strength, and physical performance in 65 frail older people, defined by Fried's criteria.[40]

- Skeletal muscle mass and type I and II muscle fibers did not change in any group.
- Muscle strength (leg extension strength) increased from 57.5 to 68.5 kg in the protein group compared with an increase from 57.5 to 63.5 kg in the placebo group.
- Physical performance (measured with the short physical performance battery) improved significantly from 8.9 to 10.0 of 12 points in the protein group, but did not change in the placebo group (from 7.8 to 7.9 points).[40]

Overall, these RCTs favor protein supplementation, which seems to delay or improve the frailty process, as measured by physical performance.

COMBINATION OF PHYSICAL EXERCISE AND NUTRITION INTERVENTIONS

Tieland and colleagues[41] explored the role of protein supplementation to augment the skeletal muscle response to resistance-type exercise training in older frail individuals.

They carried out an RCT among 62 frail older subjects (mean age, 78 years) who participated in a progressive resistance-type exercise training program (2 sessions per week for 24 weeks) during which they were supplemented twice daily with either protein (2×15 g) or a placebo.[41] The authors observed the following:

- Lean body mass increased from 47.2 kg to 48.5 kg in the protein group and did not change in the placebo group (from 45.7 kg to 45.4 kg)
- Muscle strength and physical performance improved significantly in both groups, with no added effect of dietary protein supplementation.[41]

MULTIFACTORIAL RANDOMIZED, CONTROLLED INTERVENTIONS

Numerous multidomain interventions are ongoing,[42–45] including a very ambitious international European trial,[46] but very few have been published to date. Nevertheless, an Australian team has published a series of interesting reports based on a single-center RCT on 241 frail elders (mean age, 83 years; 68% women) selected in accordance with the Fried criteria.[47,48] The intervention comprised a multifactorial interdisciplinary program targeted to address different features of frailty (including physiotherapy twice weekly, and support from a psychologist and health care worker), whereas the control group received usual care. Two hundred sixteen participants (90%) completed the 12-month study.[48] The authors observed a significantly lesser prevalence of frailty (the primary endpoint) in the intervention group compared with controls (absolute difference, 14.7%; 95% CI, 2.4–27; $P = .02$; number needed to treat, 6.8). No changes were observed between the 2 groups in terms of Barthel index, depressive symptoms, or health-related quality of life.[48]

The second report to come out of this RCT included 241 frail, community-dwelling older people without severe cognitive impairment, recently discharged from an elderly care and rehabilitation service, and was focused on:

- Gait speed
- Life Space Assessment (mobility-related disability, measured in terms of restriction on participation and limitation of activity; participation was evaluated in terms of satisfaction and performance during the preceding month)[49,50]
- Goal Attainment Scale (achievement of individualized mobility-related participation goals)[49,51]
- Reintegration to Normal Living Index (self-report measures of participation across multiple areas of life, using 9 of the 11 original criteria[49,52]).

At 12 months, the results were quite surprising in the intervention group:

- No change in gait speed
- Significant improvement in Life Space Assessment ($P<.004$)
- Significant improvement in Goal Attainment Scale ($P<.005$)
- Significant improvement in the Reintegration to Normal Living Index ($P<.0001$).[49,53]

These positive results demonstrated that focused intervention on specific frailty components yielded significant improvements, using different tools and scales that were probably closer to the patients' daily life and well-being.

Finally, these authors also performed a health-economic evaluation[54] based on the incremental cost-effectiveness ratios showing the following:

- In the overall population, the 12-month cost for 1 extra person to transition out of frailty was US$14,114 (2011 prices)

- In the subgroup of “very frail” participants, the 12-month cost for 1 extra person to transition out of frailty was US$36,525 (2011 prices).[54]

The conclusion of the Australian authors of this positive, multidomain intervention study in frail, community-dwelling older adults is that the intervention program yielded good value for money, and was particularly cost saving and cost effective in the population of very frail participants.[54]

Still, this is a fairly costly investment for any country to bear. Thus, there is a need to define simple selection processes (eg, phone selection of frail patients) and interventions (eg, e-health). A pilot study performed in Taiwan used the Chinese version of the Canadian Study of Health and Aging Clinical Frailty Scale Telephone Version (CCSHA_CFS_TV) to select frail older community dwelling participants for inclusion in the study protocol.[55] The authors reported that the CCSHA_CS_TV was an easy way to perform first stage screening of prefrail or frail older adults, with the following advantages[56]:

- It can be administrated quickly by telephone (in <2 minutes) by interviewers without formal training in geriatrics
- It has satisfactory interrater reliability and criterion validity
- The exclusion criteria are easily identified: communication barriers, too healthy or too ill, or institutionalized.

A second round of selection was subsequently performed in a local community hospital. The trial included 117 community-dwelling older adults and 122 controls selected after the phone interview (mean age, 71.4 $\pm$ 3.7 years; 59% females). Using a 2-by-2 factorial design, the participants, whose baseline characteristics were comparable, were randomly assigned to one of 3 groups:

- Exercise and nutrition (n = 55), whereby subjects received nutrition consultation/advice and 1 hour of aerobic and endurance exercise 3 times per week for 12 months.
- Problem solving therapy (PST; n = 57), comprising 6 sessions of psychological support over 3 months.
- Controls (non-exercise and nutrition [n = 62] or non-PST [n = 60]).

The global results of this study were mixed as the subjects randomized to exercise and nutrition showed:

- An improvement of their frailty state compared with non-exercise and nutrition subjects (45% vs 27%; adjusted P = .008) at 3 months, but this improvement was no longer significant at 6 or 12 months
- An increase of serum 25(OH) vitamin D level (4.9 $\pm$ 7.7 vs 1.2 $\pm$ 5.4; P = .006) at 6 months
- A lower percentage of osteopenia (74% vs 89% P = .042) at 12 months.

In the PST group, subjects showed an improvement of their frailty state at 6 months (2.7 $\pm$ 6.1 vs 0.2 $\pm$ 6.7; P = .035) and less deterioration at 12 months (-3.5 ± 9.7 vs -7.1 ± 8.7; P = .036) compared with non-PST subjects.

A recent, innovative Dutch study tested an e-health–based intervention model for frail community living elders.[57] A highly comprehensive protocol was established based on a community network including other old patients, their informal and formal care givers (general practitioners and general practitioners’ assistants, as well as community health care professionals). The intervention group (n = 290) used a health and welfare portal (called ZWIP) allowing online health communications, and 392 patients were allocated to the control group. The most important findings from this study were that:

- Only 26.2% of the participants in the intervention group actively used the online portal during the 12 months protocol
- The participants yielded a nonsignificant improvement in basic and instrumental ADL.[57]

These somewhat disappointing results obtained from a rural population in the Netherlands deserve some consideration. Perhaps the same protocol used in another context with patients more aware and adept in using modern technology might have yielded different results.

TAKE HOME MESSAGES

- Age, genetics, epigenetics (nutrition, physical exercise), and environment play key roles in the frailty process.
- The most important message concerning intervention in frail elders is that frailty may be delayed or even reversed by physical exercise, with or without nutrition supplementation, or by targeted interventions on specific frailty components. This positive conclusion is provocative, because it is becoming urgent to identify the most effective and least costly interventions to be applied to the whole aging population. Effective screening of frailty and early targeted intervention is considered key in optimizing the care of frail populations at risk by health care authorities in Europe.[58]
- A recent review of isolated or combined physical activities and nutrition interventions testified that sarcopenia, which is a major component of physical frailty, could be delayed or reversed.[14] However, it is not yet well established whether the frailty syndrome, which is much more complex than the sarcopenia syndrome, can also be delayed or reversed.

The review of the RCTs published between 2012 and 2014 on this topic does not show convincing effects of either isolated physical activities or isolated protein supplementation. The combined intervention comprising nutrition plus exercise seems to be the mainstay of frailty treatment.

- The field of multidomain interventions is promising. First results are encouraging, but the sole economic evaluation performed to date demonstrated the very high costs of such interventions.

Indeed, these findings will stimulate more research, which is surely needed to help us face the global frailty challenge as quickly as possible.

The scientific community needs to urgently address several issues:

- Define the most simple and accurate criteria to select older, community-dwelling, prefrail adults
- Implement long-term, accurately powered randomized controlled interventions
- Choose adequate tools to accurately evaluate the most relevant and important concerns of the patients, and not only scientific measurements
- Use modern technology to facilitate the entire research procedure, and empower older adults to use this technology for research purposes, but also for their own comfort and security in daily life
- Evaluate carefully the best way of increasing the cost-effectiveness of such interventions.

The twenty-first century of geriatric medicine lies ahead, and preventing sarcopenia, frailty, and their dramatic consequences is a crucial and urgent need.

ACKNOWLEDGMENTS

The authors thank Fiona Ecarnot (EA3920, University Hospital Besancon, France) for her assistance in the preparation of this manuscript.

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