Determinants of arterial gas embolism after scuba diving

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Ljubkovic M, Zanchi J, Breskovic T, Marinovic J, Lojpur M, Dujic Z. Determinants of arterial gas embolism after scuba diving. *J Appl Physiol* 112: 91–95, 2012. First published October 13, 2011; doi:10.1152/japplphysiol.00943.2011.—Scuba diving is associated with breathing gas at increased pressure, which often leads to tissue gas supersaturation during ascent and the formation of venous gas emboli (VGE). VGE crossover to systemic arteries (arterialization), mostly through the patent foramen ovale, has been implicated in various diving-related pathologies. Since recent research has shown that arterializations frequently occur in the absence of cardiac septal defects, our aim was to investigate the mechanisms responsible for these events. Divers who tested negative for patent foramen ovale were subjected to laboratory testing where agitated saline contrast bubbles were injected in the cubital vein at rest and exercise. The individual propensity for transpulmonary bubble passage was evaluated echocardiographically. The same subjects performed a standard air dive followed by an echosonographic assessment of VGE generation (graded on a scale of *0–5*) and distribution. Twenty-three of thirty-four subjects allowed the transpulmonary passage of saline contrast bubbles in the laboratory at rest or after a mild/moderate exercise, and nine of them arterialized after a field dive. All subjects with postdive arterialization had bubble loads reaching or exceeding grade 4B in the right heart. In individuals without transpulmonary passage of saline contrast bubbles, injected either at rest or after an exercise bout, no postdive arterialization was detected. Therefore, postdive VGE arterialization occurs in subjects that meet two criteria: *1)* transpulmonary shunting of contrast bubbles at rest or at mild/moderate exercise and *2)* VGE generation after a dive reaches the threshold grade. These findings may represent a novel concept in approach to diving, where diving routines will be tailored individually.

decompression sickness; arterial gas emboli

DURING A SCUBA DIVE , breathing at increased pressure results in augmented tissue gas uptake, while, during ascent, gas supersaturation (total gas tissue tension in excess of environmental pressure) commonly occurs when the ambient pressure is reduced, resulting in the formation of gas bubbles (emboli). Although common in diving, venous gas bubbles rarely produce symptoms in the form of decompression sickness (DCS), since they are carried away to the right heart and pulmonary circulation, where they are regularly eliminated by pulmonary ventilation. Sometimes venous gas bubbles can cross from the venous side to the arterial side of the circulation (arterialization), and this arterial gas embolism has been considered one of the main causes of decompression-related pathology (26). This event has usually been linked to the presence of a patent foramen ovale (PFO) (8, 23, 27), and, in a number of studies, PFO has been statistically linked to various forms of DCS (18,

28). In the absence of PFO, arterialization of gas bubbles has seldom been documented (1, 8, 20).

Recently, we reported that arterializations frequently occur after standard trimix (12) and no-decompression air dives (11) without protocol violations and in the absence of PFO. Also, the occurrence of arterializations seemed to be related with the high level of venous gas bubbling in the right heart [it appeared only if grade 4 or higher was present (on a scale of *0–5*)]. In both studies (11, 12), arterializations were present without any neurological or other symptoms of DCS, suggesting that the presence of gas bubbles in the arterial systemic circulation does not necessarily elicit acute symptoms of DCS. However, the potential chronic effects of these acutely asymptomatic arterializations are unknown. Moreover, it is unknown which anatomic/physiological pathway is responsible for this right-to-left shunting of bubbles in the absence of cardiac septal defects such as PFO. Additionally, if the magnitude of this PFO-independent bubble arterialization is comparable with that found in the presence of a large PFO, it could have the same clinical consequences and increase the risk for DCS.

For these reasons, the aim of the present study was to investigate the factors that are responsible for venous gas bubble crossover to systemic arteries in the absence of PFO in both laboratory conditions using contrast transthoracic echocardiography (TTE) and after a scuba dive in the field. Moreover, we tested whether O_2 breathing might influence the magnitude of arterialization, which has potential clinical importance in the development of preventive/therapeutic procedures after a dive.

MATERIALS AND METHODS

Study population. This study included 45 individuals (40 men and 5 women) aged 21–68 yr. At the time of the study, all participants were apparently healthy and had a valid medical certificate for diving. Their diving experience ranged from 1 to 43 yr of diving (mean: 14.8 ± 11.2 yr), and they performed from 10 to 500 h of diving annually. All experimental procedures were conducted in accordance with the Declaration of Helsinki and were approved by the Ethics Committee of the University of Split School of Medicine. Each method and the potential risks were explained to the participants in detail, and they gave written informed consent before inclusion into the study.

TTE. TTE imaging was performed by a trained ultrasonographer with subjects placed in the supine position. A phase-array ultrasonic probe (1.5–3.3 MHz) connected to a Vivid q ultrasonic scanner (GE, Milwaukee, WI) was positioned to obtain a clear apical four-chamber view of the right and left atria and ventricles. Echocardiographic recordings were stored for further analysis.

Contrast echocardiography. All participants were subjected to contrast echocardiography under laboratory conditions using agitated saline as the contrast agent (5, 11). A 20-gauge catheter was placed in the left cubital vein, and a three-way stopcock was attached with two syringes connected to its ports. One syringe contained 9 ml of saline and 1 ml of blood, and the other syringe contained 1 ml of air. The contrast bubbles, created by alternating the plunger depression six to eight times, were injected as a bolus while images were simultane-

ously obtained in the apical four-chamber view. This procedure ensured the rapid delivery of contrast bubbles to the right heart, where they were visualized as echogenic clusters. The contrast agent was injected at rest, during a Valsava maneuver, and, in some subjects, at the end of the bout of exercise performed at different intensities. After injection, the presence of contrast bubbles was examined in the cardiac cavities by TTE for a duration of 3 min. Rapid filling of left cardiac cavities with contrast bubbles within three to four cardiac cycles observed at rest or after a Valsalva maneuver was indicative of PFO. Individuals that had PFO identified were excluded from the remainder of the study (11 of 45 subjects). The delayed appearance of contrast bubbles in the left heart (after >3 cardiac cycles) indicated their passage through the pulmonary vasculature.

Exercise protocol. Subjects without detected PFO and those without significant transpulmonary passage of contrast bubbles at rest (set at grade 2) were subsequently subjected to an exercise protocol. Exercise was performed in the supine position using a stationary bicycle ergometer (Marquette Hellige Medical Systems 900 ERG, Milwaukee, WI) at two intensity levels: 30% and 50% of the calculated maximal heart rate [HR_{max}; calculated as $220 - $ age (in yr)]. HR was continuously monitored with a standard three-lead ECG. After the target HR had been reached, the exercise bout lasted for 4 min at a constant intensity. At the end of the exercise, contrast TTE was performed. If significant crossover of contrast bubbles was detected after the 30% HR_{max} exercise bout (set as grade 3), further testing at a higher exercise intensity was not performed.

O_2 administration. It has been recently reported that transpulmonary arteriovenous shunting of contrast bubbles is substantially reduced with 100% O_2 breathing (13). Therefore, in subjects with detected transpulmonary shunting of contrast bubbles, contrast TTE at rest or exercise was repeated with breathing 100% O_2. O_2 was administered through a low-resistance two-way nonrebreathing valve, which rendered the inspired O_2 at 90–95% (assessed with AMIS 2000, Innovision, Odense, Denmark). Subjects in which transpulmonary shunting was observed at rest ($n = 3$) breathed O_2 for 10 min before contrast TTE. Individuals with transpulmonary shunting of contrast bubbles during exercise repeated the same exercise protocol with continuous breathing of O_2.

Single field air dive and assessment of postdive vascular gas bubbles. A total of 34 divers performed a single no-decompression air dive to 18 m of seawater (msw) with a bottom time of 47 min. Descent and ascent rates were 10 and 9 msw/min, respectively. The dive profile was constructed with a diving computer, which was also used for monitoring the HR throughout the dive (Galileo, Uwatec, Johnson Outdoors, Racine, WI). The sea temperature at the bottom was 17–18°C, and divers were equipped with 8-mm wet suits and regularly serviced open-circuit breathing equipment. During the dive, divers performed moderate swimming at an intensity of ~30% HR_{max}. The diving procedures were performed in close vicinity to a recompression chamber facility at the Naval Medical Institute of the Croatian Navy, and a physician specialist in diving and hyperbaric medicine was present at the diving site throughout the study.

After surfacing, divers were examined by the specialist for any signs or symptoms of DCS or other diving-related pathology. Within 20 min, TTE investigation of the presence of spontaneously formed gas bubbles in cardiac chambers was commenced, and it was performed every 20 min during a time period of 120 min. Between the recordings, subjects were allowed to stand and perform a low level of activity, such as short walking or rinsing the equipment. Gas bubbles were observed and recorded in the pulmonary artery and cardiac cavities as high-intensity echoes, and their appearance in left cardiac chambers was indicative of bubble arterialization. Bubble grading was performed according to the modified scale by Eftedal and Brubakk (4). The grading system used the following definition: *0* = no bubbles; *1* = occasional bubbles; *2* = at least 1 bubble/fourth heart cycle; *3* = at least 1 bubble/heart cycle; *4* = continuous bubbling, with at least 1 bubble/cm² in all frames; and *5* = "white out," where individual bubbles cannot be seen. Recently, we (11)

proposed a subdivision of grade 4 into the following grades: *4A* = continuous bubbling, with 1–2 bubbles/cm² in all frames (same as the current grade 4); *4B* = continuous bubbling, with at least 3 bubbles/cm² in all frames; and *4C* = almost complete white out in the right heart, but individual bubbles can still be discerned. In the present study, as well, the bubble loads that met the criteria for grade 4 according to the Eftedal and Brubakk scale were further evaluated and classified into one of the recently proposed categories.

RESULTS

Anthropometric and pulmonary function data of the 34 subjects that completed the laboratory testing and the field dive were within normal limits and are shown in Table 1.

Table 2 shows the data obtained after a field dive and in the laboratory during contrast TTE. As can be inferred from the results shown in Table 2, in *subjects 1–9* we detected gas bubbles in both right and left cardiac cavities after the dive. All these individuals (*subjects 1–9*) exhibited a maximal bubble grade of 4B or higher in the right heart within 120 min after the dive. Under laboratory conditions, all of these subjects exhibited a transpulmonary passage of contrast bubbles either at rest or after mild (30% HR_{max}) or moderate (50% HR_{max}) exercise. In contrast, in *subjects 10–23*, no arterialization of gas bubbles after a field dive was found, and the maximal bubble grade detected after diving was grade 4A or less. However, similar to *subjects 1–9*, all of these individuals exhibited a transpulmonary passage of contrast bubbles in the laboratory. In *subjects 24–34*, we found no arterialization of gas bubbles after the field dive, although some of them had a high venous bubble grade (grade $\geq$ 4B) after the dive (similar to *subjects 1–9*). Also, in these individuals, no passage of contrast bubbles through the pulmonary circulation was observed in the laboratory either under resting or exercising conditions.

The grading scale used for the assessment of bubble grade after diving was also used to quantify transpulmonary shunting in the laboratory. In 9 of 23 subjects that exhibited the transpulmonary passage of contrast bubbles, breathing 100% O_2 prevented the crossover of bubbles at the same workload where the significant shunting occurred while breathing room air (as shown in Table 2). Furthermore, in 12 of 23 individuals, bubble scores were reduced when breathing 100% O_2 compared with the same level of activity when breathing air. The scores were unchanged in two individuals.

DISCUSSION

The purpose of this study was to identify the conditions that lead to the appearance of gas bubbles in the systemic circula-

Table 1. *Anthropometric and pulmonary function data for the study participants*

Parameter	Value
Age, yr	38.4 ± 11.8
Height, cm	180.3 ± 6.6
Weight, kg	88.4 ± 14.3
FVC, %pred value	113.2 ± 15.1
FEV_1, %pred value	108.5 ± 16.0
FEV_1/FVC, %pred value	97.9 ± 8.5
FEF_{25-75}, %pred value	96.5 ± 22.3

Values are means ± SD. Pulmonary function parameters are expressed as a percentage of the predicted values (%pred value). FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; FEF_{25-75}, forced expiratory flow of midexpiratory volume.

Table 2. *Bubble scores observed in the cardiac cavities after a field dive or in the laboratory*

| | Field Dive | | Transpulmonary Passage After Contrast Injection | | |
| | Maximum bubble grade (right heart) | Arterialization | Rest | 30% HR_{max} | 50% HR_{max} |
Subject					
1	4B	Yes		2	3 (1)
2	4B	Yes			3 (2)
3	4B	Yes		2	3 (0)
4	4C	Yes	1	2 (0)	NP
5	4B	Yes		2	3 (0)
6	4B	Yes		2	3 (2)
7	4B	Yes			2 (2)
8	4B	Yes		3 (1)	NP
9	4B	Yes			4A (0)
10	2	No		2	3 (2)
11	4A	No	1	3 (2)	NP
12	3	No			2 (0)
13	4A	No			3 (2)
14	3	No			2 (0)
15	1	No			3 (0)
16	3	No		2	3 (0)
17	4A	No			1 (0)
18	4A	No			2 (1)
19	4A	No		2	3 (2)
20	2	No	1	3 (1)	NP
21	3	No			2 (2)
22	2	No			3 (1)
23	4A	No			4A (3)
24	4B	No			
25	4A	No			
26	1	No			
27	4B	No			
28	4B	No			
29	4B	No			
30	4A	No			
31	4A	No			
32	4B	No			
33	4A	No			
34	4A	No			

Values in parentheses are grades with 100% O_2. After a dive, the maximal bubble grade detected in the right heart is shown. The concomitant detection of gas bubbles in the left heart is shown in arterialization. In the laboratory, grades for the contrast bubbles detected in the left heart are shown. HR_{max}, maximal heart rate; NP; not performed.

tion after diving. We found that in individuals without PFO, arterialization occurs if two prerequisites are present: *1*) a large amount of bubbles is produced postdive in the venous side of circulation (detected as a bubble grade of at least 4B in the right heart) and *2*) an individual exhibits higher susceptibility for the transpulmonary passage of gas bubbles (evidenced as a crossover of contrast bubbles to the left heart during rest or mild/moderate exercise in the absence of intracardiac shunts).

In the present study, we used a protocol for a single air field dive that is based on an algorithm commonly used in diving computers. This dive resulted in a wide range of bubble loads observed in different individuals. Divers in whom the maximal bubble load in the right heart in a postdive period did not reach grade 4B also did not arterialize at any timepoint (Fig. 1). These data are in agreement with our recent findings (11) in which a series of no-decompression air dives resulted in a relatively high incidence or arterialization, but only if a bubble grade of 4B or higher was concomitantly observed in the right heart. In the present study, among the 14 divers that scored

bubble grade 4B or higher in the right heart, the crossover of gas bubbles to the systemic circulation was found in 9 individuals.

When the data from the field are combined with laboratory testing performed with venous injections of agitated saline contrast bubbles, it is apparent that the divers with detected postdive arterialization were the same individuals that exhibited a right-to-left passage of contrast bubbles, either at rest or after performing a mild/moderate level of exercise (30% or 50% HR_{max}, respectively). In contrast, the individuals that also scored high bubble grades after a field dive (grade 4B or higher) but without apparent arterialization were those that had no evident right-to-left crossover of contrast bubbles in the laboratory under any tested condition. These findings indicate that the crossover of gas bubbles into the systemic circulation after diving (arterialization) will occur if two criteria are met. The first prerequisite is a postdiving gas bubble load reaching a threshold grade of 4B. The second prerequisite is a dive-independent individual susceptibility for the transpulmonary passage of gas bubbles. This individual propensity may be evaluated in the laboratory by a contrast TTE assessment of the potential transpulmonary passage of injected air bubbles under different conditions.

From our previous work (11) and currently ongoing experiments, we have repeatedly observed that all cases of postdive arterialization of gas bubbles are always associated with high bubble grades (grades $\geq$ 4B) in right cardiac cavities. In that regard, the arterialization does not appear to be related to the diving procedures performed, in terms of either diving depth or time. However, from our experience, in individuals who tend to arterialize after diving, when the diving procedure is modified to result with a decreased gas bubble generation after surfacing (maximal detected bubble grade in the right heart falls below a threshold grade of 4B), the arterialization does not appear (unpublished observations). These data suggest that some filtering capacity of the pulmonary vasculature might exist that needs to be exceeded for arterialization to take place.

The pathway for the passage of gas bubbles into the systemic circulation after diving has not been unequivocally identified. The possibility of gas bubbles shunting through the pulmonary microcirculation does not seem likely in view of results that the agitated saline contrast bubbles can be forced through the capillaries only with nonphysiological pressures above 300 mmHg (9, 16). A more plausible possibility is that the passage of bubbles occurs through the intrapulmonary arteriovenus anastomoses, which has been documented in the lungs of human and other species (2, 14, 22, 25). Work by others has indicated that these large-diameter vessels are, in most individuals, closed at resting conditions but become increasingly open with exercise (5), with almost all individuals opening them at the point of reaching maximal O_2 uptake ($\dot{V}_{O_2\,max}$). The exercise intensity at which these intrapulmonary shunts appear varies greatly among subjects, with some individuals exhibiting the passage of contrast bubbles already at rest or mild levels of exercise, whereas in others they become open near the level of $\dot{V}_{O_2\,max}$. The possibility of intrapulmonary shunts being the primary pathway for bubble passage is further corroborated via the use of O_2 administration. In subjects that exhibited the crossover of bubbles while breathing room air either at rest or after performing exercise, the repetition of the same procedure with concomitant breathing of O_2 prevented or reduced the appearance of contrast bubbles in the left heart. A similar
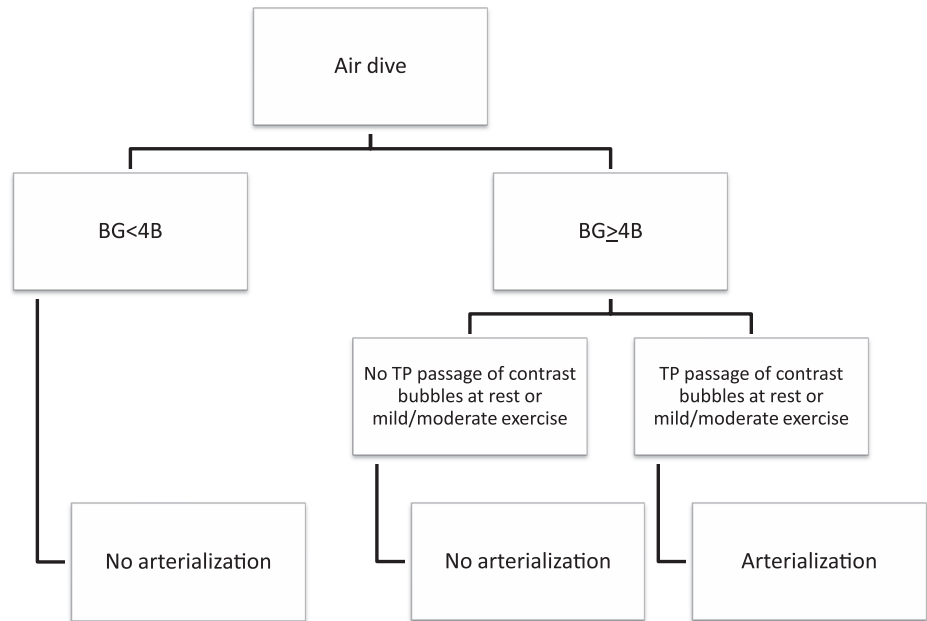
Fig. 1. Conditions leading to the arterialization of gas bubbles after a field dive. Arterialization was detected as the appearance of gas bubbles in the left cardiac cavities in a 2-h postdive period. Observations were made by transthoracic echosonography in resting subjects. BG, bubble grade; TP, transpulmonary.

effect of high O_2 administration on transpulmonary passage of glass beads injected in the pulmonary artery of anesthetized dogs has been observed in an earlier study (19) on the lung vasculature. Our findings are in agreement with this and other studies on intrapulmonary shunts in which the administration of hyperoxia also prevented or significantly diminished bubble crossover (13). Varying the gaseous component of the injected contrast bubbles (room air, 100% O_2, 100 N_2, etc.) still had the same outcome (6), indicating that the effect of O_2 on left heart bubble appearance is due to reduced blood flow through the pulmonary arteriovenous anasthomosis rather than an altered external partial pressure environment, which may affect bubble dynamics.

Our data indicate, as also shown in Fig. 1, that the high bubble grade observed in the right heart postdive is not the sole determinant of arterialization occurrence. All individuals with gas bubbles identified in the left heart postdive also exhibited the transpulmonary passage of injected contrast bubbles in the laboratory. In contrast, those individuals who had comparably high bubble loads in the right heart postdive but who did not open intrapulmonary pathways in the laboratory either at rest of after the tested levels of exercise (30% and 50% HR_{max}) did not arterialize.

The common physiological conditions responsible for the transpulmonary passage of gas bubbles after a dive and the passage of contrast bubbles in the laboratory have not been completely identified. From total of nine individuals in whom a postdive resting arterialization was detected in the supine position, only one subject exhibited a crossover of contrast bubbles through the pulmonary circulation in the laboratory at rest. In the remaining eight individuals, the crossover of contrast bubbles in the laboratory occurred at mild exercise (five subjects) or moderate exercise (three subjects). The reason that these individuals still exhibited the transpulmonary passage of gas bubbles at rest after diving is unknown. One possibility includes increased pulmonary artery pressure (PAP). The gradual increase of PAP during incremental exercise has been shown to correlate well with the opening of intrapulmonary shunts (10, 24). Since we have previously reported an increase in PAP after diving (3, 12, 15, 21), it is possible that individuals with postdive arterialization have a dive-

induced increase in PAP elevated to a similar extent as the PAP increase stimulated by exercise levels performed in the laboratory, resulting in the pulmonary vasculature becoming permeable for gas bubbles.

We found that if a diver is found to allow the transpulmonary passage of contrast bubbles under laboratory conditions at rest or after a mild/moderate exercise, he/she has a potential to arterialize at rest after diving. Whether the arterialization will occur depends on the amount of gas bubbles generated in their systemic veins. If the bubble load reaches or exceeds grade 4B in the right heart, arterialization will occur.

Despite a high incidence of arterialization postdive, no DCS was observed either in this or any of the previous diving series (11, 12). This finding may indicate that the correlation between DCS and gas bubbles in the systemic arterial circulation is not as strong as previously thought. Also, it is possible that for the DCS to occur, some critical level of arterial bubble load needs to be reached or the specific embolisation targets need to be "hit." Furthermore, the long-term effects of repetitive gas microemboli must be considered. Recently, regional functional abnormalities were identified using cerebral MRI in a population of divers that were compared with matched nondiver controls (17). The authors concluded that these changes may be partially attributed to gas microembolism and thus could explain some of the long-term clinical symptoms reported in professional divers. In addition, another study (7) reported an increased prevalence of MRI signal abnormalities among healthy military divers with detected right-to-left shunting compared with controls.

The findings of this study may represent an initial step toward a new approach to the construction of diving routines and procedures that can be tailored for each individual based on their physiological profile (propensity for bubble production and right-to-left bubble crossover). This is a new paradigm, since currently used diving profiles are based on tables and algorithms that are constructed for the entire diving population, regardless of individual characteristics. Different levels of profile freedom and conservatism, found in most diving computers, differ in the maximal time diver is allowed at a certain depth and decompression

regimes, but their choice is based exclusively on an individual assessment of one's diving skills and personal confidence. The identification of various parameters that determine the individual's predisposition to arterialize will allow a categorization of divers based on the risk of adverse impact of diving. This can be used to develop safer routines for those divers that are found to be at higher risk. For example, subjects that tend to produce high gas bubble amounts and that have permeable pulmonary pathways may benefit from using O_2 immediately after diving as it may prevent or reduce bubble crossover to the systemic circulation. Similarly, divers that produce a lot of gas bubbles but do not exhibit permeability of the lung vasculature at rest or lower levels of exercise may still arterialize if exposed to intense physical activity immediately postdive. Future research can thus be oriented toward the construction of more elaborate tests and criteria for individual risk evaluation as well as an investigation of prevention procedures, such as the effects of O_2 administration, the impact of postdive exercise on bubble passage, and the identification of divers that tend to produce more bubble than others. This should ultimately lead to safer diving, which can start at the very beginning of one's practice of this common professional and recreational activity.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M. Ljubkovic, J.Z., T.B., J.M., M. Lojpur, and Z.D. conception and design of research; M. Ljubkovic, J.Z., T.B., J.M., M. Lojpur, and Z.D. performed experiments; M. Ljubkovic, J.Z., T.B., J.M., M. Lojpur, and Z.D. analyzed data; M. Ljubkovic, J.Z., T.B., J.M., M. Lojpur, and Z.D. interpreted results of experiments; M. Ljubkovic and T.B. prepared figures; M. Ljubkovic, J.Z., J.M., M. Lojpur, and Z.D. drafted manuscript; M. Ljubkovic and J.Z. edited and revised manuscript; M. Ljubkovic, J.Z., T.B., J.M., M. Lojpur, and Z.D. approved final version of manuscript.

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