Preliminary study about the relationship between estimated training status and RAS polymorphisms on blood pressure and ACE activity in the elderly

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Abstract

Objective: Polymorphisms of the renin angiotensin system (RAS) are associated with increases in blood pressure (BP). Physical exercise has been considered the main strategy to prevent this increase. This study aimed to investigate the relationship between estimated training status (TS), BP and angiotensin-converting enzyme (ACE) activity in elderly people classified as low or high risk to develop hypertension according to genetic profile.

Methods: A total of 155 elderly participants performed the following assessments: general functional fitness index (GFFI), systolic BP (SBP) and diastolic BP (DBP), blood collection for ACE activity and analyses of the RAS polymorphisms.

Results: Uncontrolled hypertensive (UHT) participants presented higher values of SBP and DBP compared with normotensive (NT) and controlled hypertensive (CHT) participants. No differences were found in ACE activity and GFFI between groups. In the high risk group, UHT presented higher values of SBP and DBP compared with other groups. CHT presented higher values of SBP compared with NT. Furthermore, UHT presented higher values of ACE activity compared with CHT and lower values of GFFI compared with NT.

Conclusion: MDA, TIA and TIC genetic combinations were associated with high risk of developing hypertension while the maintenance of good levels of TS was associated with lower BP values and ACE activity.

Keywords

Polymorphisms, RAS, blood pressure, physical fitness, elderly

Date received: 1 December 2017; accepted: 8 May 2018

Introduction

The renin-angiotensin aldosterone system (RAS) plays an important role in cardiovascular homeostasis, especially in the vascular tonus. An increase in the activation of RAS may result in increased vasoconstriction and, consequently, increased total peripheral resistance and high blood pressure (BP), especially in the elderly. Also, increased RAS activity has been associated with polymorphisms, thus justifying the genetic influence on the etiology of hypertension.

As result of this relationship, studies have shown associations between RAS polymorphisms and cardiovascular disease (CVDs), including hypertension. Furthermore, according to Rola and Ferreira, there is evidence that RAS
genetic polymorphisms may influence the development and maintenance of hypertension and CVDs; however, no relationship has been shown in elderly populations.7–10

In contrast, regular physical exercise is recommended for the maintenance of health and prevention of hypertension and CVDs. The 2008 Physical Activity Guidelines for Americans states that, for most health outcomes, additional benefits occur when the amount of physical activity increases through higher intensity, greater frequency, and/or longer duration.11 A 2010 systematic review also critically examined whether this dose-response relationship exists for the primary prevention of hypertension.12

Additionally, Matarelli et al. showed that moderate-to-intense exercise, aerobic and/or resistance, are associated with significant reductions of cardiovascular events.13 Briefly, physical exercise is considered an important strategy for prevention and treatment of these diseases.13–16

Although the relationship between RAS polymorphism and hypertension and between physical exercise and hypertension are already established in the literature, there is no strong evidence about the relationship between combinations of RAS polymorphisms, hypertension, and physical exercise.

There are just a few studies that have sought to establish this relationship, such as that of Jones et al. which demonstrated a potential interaction of the ACE I/D and the AGT M235T gene polymorphisms and exercise training on changes in ambulatory BP in African American hypertensives.17 Only subjects with the ACE II genotype group demonstrated a significant increase in sodium excretion, which was inversely related with changes in 24-h diastolic and mean BP after short-term exercise training.

In addition, Montrezol et al. showed a reduction on BP in homozygous ACE (I/D) genotypes and no changes in I alleles carriers after a resistance training programme,18 and Pescatello et al. observed the angiotensinogen-converting enzyme (ACE), angiotensin type 1 receptor (AGTR1), aldosterone synthase (CYP11B2), and adducin (ADD1) genes exhibited intensity-dependent associations with the ambulatory BP and postexercise hypotension (PEH) response after acute exercise.19 However, this effect was observed after vigorous, but not moderate intensity exercise among African Americans.

Although these relationships have already been studied individually, as previously noted, there is limited evidence about the relationship between the combination of RAS polymorphisms, hypertension and physical exercise. Moreover, different results can be found due to the differences in type, intensity, frequency and duration of the physical exercise performed. Thus, it seems reasonable to suggest evaluation of estimated training status (TS) instead of the kind of physical exercise performed.

Briefly, different combinations of polymorphisms (genotype, allele and combination between them) can expose adults and elderly subjects to a higher or lower risk of developing hypertension; however, how the estimated TS may interfere with this association remains unclear. Thus, the purpose of this study was to investigate the relationship between estimated TS, BP values and the activity of ACE in elderly subjects, classified as low or high risk of developing hypertension according to genetic background (allele, genotype and possible combinations).

Methods

Screening

This was a transverse study, which was attended by 155 participants (66.94 ± 6.83 years) from Bauru, São Paulo, Brazil. Written consent was provided at the beginning of the experiment and the Institutional Review Board of UNESP - São Paulo State University (CEP/FC-UNESP no. 323.427) previously approved all procedures.

Participants were recruited through personal invitations, flyers, groups of seniors from university extension projects or municipal programs held by City Hall of Bauru. BP values and antihypertensive drugs were considered for group division. Participants with values lower than 139 mmHg for systolic BP (SBP) and/or 89 mmHg for diastolic BP (DBP), with no use of antihypertensive medicine, were classified as the normotensive (NT) group, while participants with BP values higher than 140 mmHg for SBP and/or 90 mmHg for DBP, or with normal level of BP controlled by antihypertensive medication were classified as the hypertensive (HT) group. This classification was used for allele and genotype evaluation and combinations of the RAS polymorphisms.

To be included in the study, all participants had to meet the following criteria: non-smoking, non-alcoholic (<3 drinks/beers per day), should not have cardiovascular, peripheral, cerebrovascular, neurologic or psychiatric diseases. Also, they should not be under treatment with medications that affect glucose metabolism or renal hemodynamics and not have any medical or orthopedic condition that could affect their ability to successfully participate in a physical exercise battery test.

Clinical evaluation

Resting BP was measured according to the VII Brazilian Guidelines of Hypertension,20 with an adequate aneroid sphygmomanometer (Wan Med®) and stethoscope (Littmann®). For nutritional status, body mass index (BMI) and waist hip relationship (WHR) were used.21,22

Biochemical analysis

Blood samples were collected in EDTA vacutainer tubes after breakfast and 2 h fasting in the morning. Venous blood (10mL) was collected through the antecubital vein,
fractioned as whole blood and plasma samples, and then stored and kept in the freezer (–80°C) for further analysis. During blood collection, care was taken to avoid hemolysis of blood. However, if hemolysis occurred, a new data collection time was scheduled for that participant.

Total blood (5 mL) was used for DNA extraction (QIAamp DNA Mini Kit, catalog number 51154, Qiagen®, Hilden, Germany) and subsequent analysis of the M235T polymorphism of the angiotensinogen gene (rs699); D/I of the ACE gene (rs1799752); A1166C of angiotensin II type 1 receptor (AT1R) gene (rs5186) were made by real-time polymerase chain reaction (Taqman® system in thermocycler, Viia7, Applied Biosystems®, Foster City, CA) followed by enzymatic restriction (rs5186 and rs699) and separation on an electrophoresis gel (rs1799752).23–25

The possible combinations between RAS polymorphisms are presented in Table 1. Combinations with frequencies lower than 5% in any group were excluded from the statistical analysis.

Based on RAS polymorphisms combinations, all participants were classified as low risk and high risk according to their risk of developing hypertension. To avoid the influence of antihypertensive medicine in the analysis, the HT group was further divided into two subgroups: controlled hypertensive (CHT), which included HT participants with BP level controlled by medication, and uncontrolled hypertensive (UHT), which included HT participants who had high BP values and no use of medication.

The remaining 5 mL blood was centrifuged at 4000 rpm for 5 min and the plasma used for the measurement of plasma ACE activity, determined by fluorometric assay using Hippuryl-His-Leu (Sigma) as substrate.26 Briefly, 10 µL of heparinized plasma were incubated with 210 µL of Tris buffer (Tris 20 mol/L, NaCl 0.3 mol/L, pH 8.1) containing Hip-His-Leu (1 mmol/L) at 37°C for 20 min. NaOH 0.5 mol/L (1 mL) was used to stop the reaction. Then, 100 µL of OPA (o-phthalaldehyde) was added and homogenized for 4 min. HCl 6 mol/L (200 µL) was also added and the solution was centrifuged at 3000 rpm for 5 min. Supernatants were placed in a 96-well microplate and fluorescence was detected at 365 nm excitation and 495 nm emission. Standard curves for His-Leu were used to calculate ACE activity (nmol/min/mL).27

### Estimated TS

The assessment of estimated TS was carried out through functional fitness battery test proposed by the American Alliance for Health Physical Education Recreation and Dance (AAHPERD), which evaluated the following capacities: coordination, flexibility, muscular strength and endurance, dynamic agility, and cardiovascular endurance as previously described.28 The sum of the percentile of each test was used to calculate the GFFI, as previously described by Zago and Gobbi, Benedetti et al., and Mazo et al.29–31

### Statistical analysis

The distribution of genotypes and alleles for each polymorphism was evaluated by the Hardy-Weinberg equilibrium using the Chi squared test ($\chi^2$) (StatView, Cary, NC). A priori, unusual genotypic combinations of the RAS polymorphisms, with frequency less than 5%, were excluded from the analysis. This procedure is to reduce the degrees of freedom and increase the power of the analysis. Data were reported as mean and SD, with a significance level of $p < 0.05$. The Kolmogorov-Smirnov (KS) test was used to check normal distribution of data and ANOVA with Tukey post-test was used for mean comparison. BP and TS were considered as independent variables. Data were analyzed using the SPSS 20.0 statistical package.

To calculate the sample size, the Bonfarine and Bussab formula was used.32 The estimated prevalence of hypertension was 51% and the estimated elderly population in Bauru-SP was 42,234. A significance level of 5% and a tolerable absolute error of 8% were adopted. Therefore, a representative sample of this population reached a total number of 150 participants.

### Results

Table 2 shows the characteristics of the participants classified as NT and HT. A predominance of female participants can be observed but no difference was found between the HT and NT groups. HT participants showed higher values of BP (SBP and DBP) compared with NT. No difference was found in functional capacity between NT and HT groups. Although HT presented higher values of BMI and WHR compared with NT, both groups were classified as overweight. Moreover, no difference was found in plasma ACE activity between NT and HT groups.
It is important to highlight that 10.46% of participants in the HT group did not use antihypertensive drugs; however, 25.58% used ACE inhibitors and 63.96% used other drugs (Table 2). Chi-Square analysis showed a difference between the NT and HT groups for medication use; however, although the number of participants taking antihypertensive medication is different, ANOVA one-way analysis revealed that SBP values were similar between groups (no drugs: $137.80 \pm 14.44$ mm Hg; ACE inhibitors: $125.04 \pm 11.50$ mm Hg and other drugs: $126.38 \pm 13.33$ mm Hg). However, DBP was different between no users ($91 \pm 3.16$ mm Hg) compared with ACE inhibitors users ($77.56 \pm 8.97$ mm Hg). These data showed similar results between ACE inhibitor and other drugs groups, thus suggesting no influence of different type of medications on BP values.

Table 3 shows the distribution of alleles and genotypes for RAS polymorphism in NT and HT individuals. For AGT polymorphism, a greater frequency of ancestral allele (D) in NT (57%) and HT group (49%) and a predominance of the heterozygous (ID) genotype for both groups (51% and 52%, respectively) were observed. For the AT1R polymorphism, both groups had a higher frequency of the ancestral allele (A) (79% and 74%, respectively) and a greater prevalence of ancestral homozygous genotype (64% and 65%, respectively).

However, no statistical differences were observed among genotypes and allele regarding the risk of developing high BP.

In general, when RAS polymorphisms (AGT, ACE, and AT1R) were analyzed independently (allele or genotype), no difference was found between NT and HT groups (Table 3). However, when the combinations between polymorphisms were analyzed (Table 4), statistical differences were observed in MDA, TIA, and TIC. These results suggest a possible presence of high risk of hypertension in these specific combinations (MDA, TIA, and TIC) and low risk for MIA, MDC, TDA, and TDC combinations. In addition, a higher frequency of MIA (31%) in the NT group and MDA (33%) in the HT group was observed.

As expected, BP was higher in HT compared with NT for SBP ($120 \pm 11$ versus $124 \pm 13$ mm Hg, for NT and
HT, respectively, \( p < 0.009 \) and DBP (75 ± 8 versus 77 ± 8 mm Hg, for NT and HT, respectively, \( p < 0.04 \)). However, to discriminate the influence of antihypertensive medicine on the analysis, each group was subdivided according to the following categories: NT, CHT, and UHT. Figures 1 and 2 present BP values, ACE activity and GFFI according to hypertensive status of low or high genetic risk profile, respectively. It can be observed that the UHT group presented higher levels of SBP and DBP compared with the NT and CHT groups. No differences were found in ACE activity and GFFI between groups. Regarding the population with high risk of developing hypertension (Figure 2),

### Table 3. Distribution of genotypes and alleles of the RAS gene polymorphism in normotensive and hypertensive elderly.

| Alleles/genotypes | Normotensive (n = 69) | Hypertensive (n = 86) | p-value | Odds ratio (95%CI) |
|-------------------|-----------------------|-----------------------|---------|-------------------|
| **AGT**           |                       |                       |         |                   |
| M                 | 0.56 (77)             | 0.54 (92)             | –       | 1.00 (reference)  |
| T                 | 0.44 (61)             | 0.46 (80)             | 0.685   | 1.09 (0.69–1.72)  |
| MM                | 0.28 (19)             | 0.29 (25)             | –       | 1.00 (reference)  |
| MT                | 0.56 (39)             | 0.49 (42)             | 0.594   | 0.81 (0.39–1.71)  |
| TT                | 0.16 (11)             | 0.22 (19)             | 0.575   | 1.31 (0.50–3.40)  |
| **ACE**           |                       |                       |         |                   |
| I                 | 0.43 (59)             | 0.51 (87)             | –       | 1.00 (reference)  |
| D                 | 0.57 (79)             | 0.49 (85)             | 0.170   | 0.72 (0.46–1.14)  |
| II                | 0.17 (12)             | 0.24 (21)             | –       | 1.00 (reference)  |
| ID                | 0.51 (35)             | 0.52 (45)             | 0.468   | 0.73 (0.31–1.69)  |
| DD                | 0.32 (22)             | 0.24 (20)             | 0.166   | 0.51 (0.20–1.32)  |
| **AT1R**          |                       |                       |         |                   |
| A                 | 0.79 (109)            | 0.74 (138)            | –       | 1.00 (reference)  |
| C                 | 0.21 (29)             | 0.26 (34)             | 0.786   | 0.92 (0.53–1.61)  |
| AA                | 0.64 (44)             | 0.65 (56)             | –       | 1.00 (reference)  |
| AC                | 0.30 (21)             | 0.30 (26)             | 0.938   | 0.97 (0.48–1.95)  |
| CC                | 0.06 (4)              | 0.05 (4)              | 0.742   | 0.78 (0.18–3.32)  |
| **χ²** = 1.95     |                       |                       | P = 0.375 |                   |

Frequencies and the gross values of each allele and genotype: % (n); CI: 95% confidence interval; P-value was considered significant when <0.05 (alleles/genotypes).

### Table 4. Distribution of combination of RAS polymorphisms in normotensive and hypertensive elderly.

| Genetic combination | Normotensive (n = 69) | Hypertensive (n = 86) | p-value | Odds ratio (95%CI) |
|---------------------|-----------------------|-----------------------|---------|-------------------|
| MIA                 | 0.31 (43)             | 0.16 (27)             | –       | 1.00 (Reference)  |
| MDA                 | 0.14 (20)             | 0.33 (57)             | 0.0004*** | 4.56 (1.91–10.89) |
| MDC                 | 0.09 (12)             | 0.01 (3)              | 0.306   | 0.43 (0.08–2.23)  |
| TIA                 | 0.10 (13)             | 0.20 (34)             | 0.005*** | 3.87 (1.46–10.22) |
| TIC                 | 0.01 (1)              | 0.12 (20)             | 0.0001*** | 38.75 (4.75–315.7) |
| TDA                 | 0.24 (33)             | 0.12 (21)             | 0.946   | 0.96 (0.38–2.42)  |
| TDC                 | 0.10 (14)             | 0.03 (6)              | 0.451   | 0.58 (0.13–2.41)  |
| Excluded            | 0.01 (2)              | 0.02 (4)              | –       | –                 |
| **χ²** = 37.33      |                       |                       | P = 0.0001*** |                   |

Frequencies and the gross values of participants are shown in % (n); CI: 95% confidence interval; P-value was considered significant when <0.05 (combination of RAS polymorphisms).
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UHT presented higher values of ACE activity compared with CHT and lower values of GFFI compared with NT.

Discussion

The purpose of this preliminary study was to investigate the influence of RAS polymorphism combinations on the risk of developing hypertension, and if different levels of estimated TS could influence the values of BP and ACE activity in elderly. According to the findings of this present study, GFFI is the variable that seems to exert more influence on the hemodynamic and biochemical variables of individuals at high risk of developing hypertension.

Table 1 shows the characteristics of the participants and a comparison between the NT and HT groups. As expected, HT presented high levels of BP compared with the NT group, even though they were taking antihypertensive medicines. Moreover, differences were found in BMI and WHR, i.e. the HT group had higher values compared with the NT group. This result is in accordance with those of Gonçalves et al., who found that increased BMI was proportionally found among HT patients (63.4%) compared with NT patients (46.7%).

The relationship between the combination of RAS polymorphisms and hypertension is still not well established in the literature. Some studies show associations of some polymorphisms with HT and CVDs, while others studies indicated that hypertensive people have an unfavorable relationship with health variables. In agreement, the Brazilian Society of Hypertension also shows a relationship between high BP and high levels of BMI and WHR. However, it is important to note that in the current study, although there were differences between groups, both groups were in the same classification of overweight.

It is also interesting to note the large number of women (133) compared with men. Nevertheless, the statistics tool did not identify differences among them. In accordance with this, the study of Trapé et al. showed that this predominance is expected because women are more engaged in social, community and supervised programs of fitness, whereas men have lower health concerns, which explains the lower participation of men in health research.

As far as RAS polymorphisms, no significant differences were found in alleles and genotypes between groups. However, in the analysis of RAS polymorphism combinations, it was observed that MDA, TIA, and TIC were significantly more frequent in the HT group. This suggests that carriers of these combinations may have a higher risk of developing hypertension when compared with other groups, such as MIA, MDC, TDA, and TDC.

The relationship between the combination of RAS polymorphisms and hypertension is still not well established in the literature. Some studies show associations of some polymorphisms with HT and CVDs, while others studies

**Figure 1.** Hemodynamics variables, ACE activity and estimated TS related to BP groups of the older population with low risk (no risk) of developing hypertension (n = 155) according to the genetic profile (MIA, MDC, TDA, and TDC combinations). Values are expressed as mean and SD. (a) SBP; (b) DBP; (c) ACE activity (nmol/min/mL); (d) GFFI scores. *p < .05. ACE: Angiotensin-converting enzyme; TS: training status; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; GFFI: general functional fitness index.
did not.\textsuperscript{10,36} For instance, Freitas et al. did not find association between M235T polymorphisms of angiotensinogen, D/I ACE and A1166C AT1R with HT in 160 Brazilian participants.\textsuperscript{10} Fortunato et al. also demonstrated no association between ACE (I/D), AGT (M235T), AT1R (A1166C), MTHFR (C677T) gene polymorphisms and anthropometric, clinical, and laboratory parameters in a well-defined (in regards to health and nutritional status and lifestyle) population of young trained participants from Southern Italy.\textsuperscript{36} However, in this latter study, MTHFR (C677T) polymorphism was significantly associated with lower hemoglobin plasma levels in TT compared with CC+CT females.\textsuperscript{36}

Conversely, a study by Agachan et al., performed with 194 Turkish participants, found an association of TT genotype of M235T polymorphism of angiotensinogen and of D allele of the polymorphism D/I of ACE with CVDs.\textsuperscript{35} In addition, Firouzabadi et al. evaluated the relationship between six RAS gene polymorphisms and CVDs in an Iranian population.\textsuperscript{8} The authors concluded that TT genotype of ACE A-240T seems to promote a major genetic risk factor for CVDs.\textsuperscript{8} Miao and Gong, also demonstrated an association between ACE gene deletion/insertion polymorphism and risk of hypertension in 45 case-control studies including 10,236 subjects.\textsuperscript{9}

Considering physical exercise in these relationships, Alves et al. investigated the effects of the interaction between aerobic exercise training (AET) and ACE I/D polymorphism on ACE N- and C-domain activities and vascular reactivity in humans.\textsuperscript{37} At baseline (pre-training), all variables were similar among the three genotypes. However, after exercise, similar increase in vascular reactivity, VO\textsubscript{2} peaks were observed in all three genotypes. Moreover, there were no changes in heart rate and BP. However, the DD genotype was associated with greater ACE and C-domain activities both pre- and post-training. Exercise decreased the total ACE and C-domain activities similarly in all genotypes, while increasing N-domain activity in the II and DD genotypes. However, interestingly, the measurements of N-domain activity after training show greater activity compared with other genotypes. These results suggest that vasodilation in response to exercise may be associated with a decrease in total ACE and C-domain activities, regardless of genotype, and the increase in N-domain activity is dependent on the DD genotype.

In addition, Goessler et al. investigated the role of ACE2 polymorphisms in PEH and observed a significant reduction in SBP and DBP following exercise in individuals AA/AG for the Int-1 polymorphism (p-interaction = 0.02 and 0.001, respectively), whereas this could not be found in homozygous individuals G (p-interaction = 0.76 and 0.51, respectively).\textsuperscript{38} Individuals AA/AG for the Int-3 polymorphism showed a significant reduction in SBP following exercise (p-interaction = 0.02). These results

![Figure 2](image-url)

**Figure 2.** Hemodynamics variables, biochemical analysis and estimated TS related to BP groups of the older population with higher risk of developing hypertension (n = 155) according to the genetic profile (MDA, TIA and TIC combinations). Values are expressed as mean and SD. (a) SBP; (b) DBP; (c) ACE activity (nmol/min/mL); (d) GFFI scores. *p < 0.05. ACE: Angiotensin-converting enzyme; TS: training status; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; GFFI: general functional fitness index.
demonstrated the interference of ACE2 polymorphism in PEH. An additional study from Goessler et al. investigated the acute effect of a single walk on BP and tested whether polymorphisms of the ACE gene could explain the variation in BP responses. The authors concluded that PEH may occur after a walk at moderate intensity in I allele carriers; however, this effect was not demonstrated in DD allele carriers. These results highlighted that ACE gene genetic variation might affect BP response to exercise.

In the current study, no association with HT was found when the polymorphisms AGT, ACE, and AT1R were analyzed separately. However, MDA, TIA, and TIC combinations of RAS polymorphism were associated with increased risk of developing HT. Taking into account these results, participants were divided into two groups, i.e. low or high genetic risk of developing HT. Moreover, each group was subdivided according to the hypertension status (BP level and medicine consumption, as aforementioned). It was observed that, in the low genetic risk group, there were differences only in the hemodynamic variables (SBP and DBP), which is consistent with the idea of lower activation of RAS system in these subjects.

Interestingly, among the low genetic risk subjects there were some participants classified as HT. Brazilian census data (IBGE) estimate that, among people considered as high risk, more than 20% will have some cardiovascular event in the next 10 years, while among people classified as high risk, more than 20% will have some cardiovascular event.

Another interesting observation is that participants classified as high risk of developing HT presented some differences in both ACE activity and the levels of estimated TS between groups that was not present in low genetic risk subjects.

Sedentary lifestyle is currently considered a major risk factor for CVDs and is also related to a higher risk of developing HT.40 It can be observed in the current study that the group classified in the category of HNC had lower levels of TS compared with NT group. This suggests that keeping good levels of TS may beneficially influence the cardiovascular system and prevent increases of BP in the elderly.

Conclusion

Regarding RAS polymorphisms (AGT, ACE, and AT1R), it was observed that MDA, TIA, and TIC combinations were associated with high risk of developing HT. Besides, in carriers of these combined polymorphisms, the maintenance of good levels of TS was associated with lower BP values and ACE activity.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by São Paulo Research Foundation (FAPESP) grants nos. 2015/24847-8 to ASZ and 2015/03965-2 to CFS.

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