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Evaluation of Cerebral Oxygenation and Tissue Perfusion in Patients Ongoing Coronary Artery Surgery with Cardiopulmonary By-pass

Kardiyopulmoner Baypas ile Koroner Arter Cerrahisi Uygulanan Hastalarda Serebral Oksijenizasyonun ve Doku Perfüzyonunun Değerlendirilmesi

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ABSTRACT Objective: We aimed to determine whether there is a correlation between perfusion parameters [Lactate (lac), venoarterial carbondioxide gradient (ΔpCO_2), central venous oxygen saturation ($ScVO_2$)] and the relationship between these parameters and cerebral oxygenation in normothermia (T_2), hypothermia (T_3) and re-warming (T_4) periods in cardiopulmonary bypass procedure (CPB). **Material and Methods:** Forty patients aged 19-78 years who were scheduled for elective coronary artery bypass surgery were included in the study. Mean arterial pressure (MAP), cerebral oxygenation (rSO_2), periferic oxygen saturation (SpO_2) values were recorded and by taking blood samples from arterial cannula and central venous catheter simultaneously; hematocrit (Htc), ΔpCO_2, lac, $ScVO_2$, actual base excess (aBE), bicarbonate (HCO_3) values were recorded in T1 (after anesthesia induction and central venous catheterization), T_2 (normothermia, 36°C, at the start of CPB), T_3 (hypotermia, 32°C) and in T_4 (at the end of CPB, rewarming, 36°C). **Results:** Between ΔpCO_2-lac values, only positive correlation was found in T_4 and there was no correlation between them at other times. There was significant negative correlation between rSO_2 and lac in T1, T_3 and T_4, but no significant correlation was found between rSO_2-ΔpCO_2 parameters at any time. The correlations of lac and ΔpCO_2 with cross-clamp and CPB durations were positive, whereas the correlations between $ScVO_2$ and rSO_2 with cross-clamp and CPB durations were negative. **Conclusion:** ΔpCO_2 is not an early indicator of hypoperfusion in patients undergoing CPB in accordance with the literature and the lactate level is a guiding parameter in reporting the perfusion status. We recommend the intraoperative use of cerebral oximetry to prevent the brain from being affected by hypoperfusion during CPB and to prevent postoperative neurocognitive disorders in patients.

Keywords: Cardiopulmonary by-pass; cerebral oximeter; perfusion; coronary artery surgery

ÖZET Amaç: Çalışmamızda; kardiyopulmoner bypass (KPB) esnasında normotermi, hipotermi ve yeniden ısınma dönemlerinde perfüzyon parametrelerinin [Laktat (Lac), venoarteryel karbondioksit basınç farkı (ΔpCO_2), santral venöz oksijen saturasyonu ($ScVO_2$)] kendi aralarında korelasyonunun olup olmadığını ve serebral oksijenizasyon ile ilişkisini ortaya koymayı amaçladık. **Gereç ve Yöntemler:** Çalışmaya elektif koroner arter by-pass cerrahisi planlanan, 19-78 yaş arası 40 hasta dahil edildi. Anestezi indüksiyonu sonrası santral ven kateteri takıldıktan sonra (T_1), KPB başlangıcında normotermi (36°C) döneminde (T_2), KPB hipotermi (32°C) döneminde (T_3) ve KPB sonu yeniden ısınma (36°C) döneminde (T_4) hastanın ortalama arteryel basınç (OAB), serebral oksijenizasyon (rSO_2) değerleri ile hastanın arteryel kanülünden ve santral ven kateterinden eş zamanlı alınan kan gazı örneklerinden ortalama periferik oksijen saturasyonu (SpO_2), hematokrit (Htc), venöz ve ΔpCO_2, lac, $ScVO_2$, aktüel baz açığı (aBE), bikarbonat (HCO3) değerleri kaydedildi. **Bulgular:** ΔpCO_2-lac değerleri arasında sadece T_4'de pozitif yönlü korelasyon varken diğer zamanlarda aralarında korelasyon bulunmadı. rSO_2-lac arasında T_1, T_3 ve T_4'de negatif yönlü korelasyon anlamlı bulunurken, rSO_2-ΔpCO_2 parametreleri arasında ise zamanların hiçbirinde anlamlı korelasyon bulunmadı. Lac ve ΔpCO_2'nin kross-klemp süresi ve KPB süresi ile korelasyonları pozitif yönlü iken, $ScVO_2$ ve rSO_2'nin kross-klemp ve KPB süreleri ile arasındaki korelasyonlar negatif yönlü bulunmuştur. **Sonuç:** ΔpCO_2'nin, literatürle uyumlu olarak, KPB uygulanan hastalarda hipoperfüzyonun bir erken belirteci olmadığı ve laktat düzeyinin perfüzyon durumunu bildirmede yol gösterici bir parametre olduğu kanaatindeyiz. Beynin KPB esnasındaki hipoperfüzyondan etkilenmemesi için ve hastalarda postoperatif nörokognitif bozukluklar gelişmemesi için intraoperatif serebral oksimetre kullanımını önermekteyiz.

Anahtar Kelimeler: Kardiyopulmoner bypass; serebral oksimetre; perfüzyon; koroner arter cerrahisi

Cardiopulmonary by-pass (CPB) is a technique that has been used for nearly 70 years and is preferred in many major cardiac surgeries. The aim of the CPB is to carry oxygen (O_2) to tissues and eliminate carbon dioxide from the tissues (CO_2) to provide adequate oxygenation to the tissues during surgery. Hypoxia may occur during CPB, even if adequate hematocrit (Htc), partial oxygen pressure (pO_2), and mean arterial pressure (MAP) are provided. This may be due to pre-operative cardiac instability or systemic diseases associated with existing cardiac pathology.[1] To assess adequate tissue perfusion; pO_2, partial CO_2 pressure (pCO_2), Htc, actual base excess (aBE), bicarbonate (HCO_3), lactate (lac) values, and central venous O_2 ($ScVO_2$), veno-arterial CO_2 gradient (ΔpCO_2) are used in blood gas analysis. In particular, the blood lactate level has vital importance in evaluating perfusion during CPB.[2,3]

Venous CO2 level and ΔpCO2 are expected to increase when the blood circulation is impaired or stopped. In cases of severe sepsis in which perfusion is impaired, and severe pulmonary embolism in which pulmonary circulation is impaired, or in cases of traumatic shock, ΔpCO_2 level increases.[4] In CPB, systemic and pulmonary circulation decreases/stops and hypoperfusion status are seen.[5] However, ΔpCO_2 is not a parameter that accurately reflects tissue perfusion alone. However, it gives an idea about perfusion indirectly.

Near-infrared spectrometer (NIRS) technique shows the target organ oxygenation and perfusion by reflecting the capillary sample without requiring pulse and current. In the study, the balance between cerebral oxygen delivery and consumption during CPB was followed by a cerebral oximeter operated by NIRS method.[6] We aimed to determine whether there was a correlation between perfusion parameters (Lac, ΔpCO_2, $ScVO_2$) during CPB and their relationship with cerebral oxygenation. Also by aiming this, we researched whether there is a relationship between CO_2 solubility and other perfusion parameters in hypothermia period.

MATERIAL AND METHODS

Ethics committee approval and consent of the patients were taken for the study with the decision dated 08/01/2019 and numbered 2019-01/04. This study is designed on principles of Helsinki Declaration properly. Forty patients aged between 19-78 years who were scheduled for elective coronary artery bypass surgery between 10/01/2019 and 20/02/2019 were included in the study. For premedication, all patients were given diazepam orally (diazem, DEVA®) at a dose of 0.15 mg/kg 12 hours before the operation and intramuscular 0.1 mg/kg midazolam (dormicum, DEVA®) 30 minutes before the operation was enjected. After the cases were taken to the operation room, demographic data such as age, height, weight, body surface area were recorded. Also echocardiographic data such as ejection fraction, left atrium diameter, left ventricle diastolic diameter values were recorded. CPB duration and cross-clamp duration were also recorded. Before starting the anesthesia induction, ECG electrodes were inserted and connected to the monitor for D2-V5 leads and for pulse oximetry monitoring. The regional oxygen saturation (rSO_2) (somatenic regional oxymetry, brand: INVOS; Covidien) probe was unilaterally adhered to the fronto-temporal region.[7] When the rSO_2 values decreased below 60% or there was a 20% decline from baseline values, hemodynamia, pump flow, hemoglobin and oxygenation were checked. These values were taken as cut-off for cerebral desaturation. The left cephalic or brachial vein was cannulated with a 16 G catheter. The right radial artery pressure was monitored by cannulation with a 20 G catheter. Patients were ventilated with 100% O_2. All patients were standardized by anesthesia induction of 10-15 mcg/kg fentanyl citrate intravenous (IV), 3 mg/kg thiopental sodium (pentothal, ABBOTT®) iv, 0.5 mg/kg rocuronium bromide (myocron, VEM®) iv. After adequate anesthesia depth and muscle relaxation were achieved and patients were intubated with appropriate endotracheal tube and were connected to the mechanical ventilator (datex-ohmeda) in volume control mode. Normocapnic ventilation was achieved with tidal volume 7 ml/kg, respiratory rate: 12/min, Ti/Te: 1/2, PEEP: 0 Mbar using 50% O_2 to 50% air mixture.

The right internal jugular vein was cannulated with Seldinger method under sterile conditions as CPB routine under ultrasonography. Central venous pressure was monitored from the central catheter and was replaced with fluid and blood product when necessary. In the maintenance of anesthesia, midazolam 0.05 mg/kg/h and remifentanyl (Glaxo Smith Kline®) were administered as an infusion of 0.03 mg/kg/h in IV infusion and sevoflurane (ABBOTT®) at a concentration of 2% as an inhalation anesthetic. Isosorbide mononitrate (perlinganit, MELUSIN®) infusion was used in hypertensive patients and dopamine hydrochloride (dopamine, FRESENIUS KABI®) infusion was used in hypotensive patients and in order to prevent MAP below 60 mmHg. After excision of the left internal thoracic artery, heparin was administered at a dose of 300 IU/kg and active coagulation time (ACT) was maintained between 450-600 seconds. CPB was initiated after cannulation. The pump flow was maintained at 2-2.5 L/m²/min during the operation. Body temperature was kept at 32°C in all patients. Cold crystalloid cardioplegia after cross-clamp was given at a dose range of 7-10 ml/kg. Midazolam and remifentanyl infusions were continued until skin closure. Cross-clamp was removed following distal anastomosis. If heart does not work spontaneously, it was worked by defibrillation. Proximal anastomosis was done by using partial clamp to aort if necessary and after completing coronary revascularization, patients with appropriate blood pressure and cardiac rhythm were removed from CPB.

After central venous catheterization (T1), during the period of normothermia (36°C) at the onset of CPB (T2), during hypothermia (32°C) period (T3) of CPB and in rewarming period of CPB (36°C) (T4); the patient's MAP, mean peripheral oxygen saturation (SpO_2), cerebral oxygenation (rSO_2) values were recorded and by taking blood samples from arterial cannula and central venous catheter simultaneously Htc, venous and arterial carbon dioxide gradiant pressures (ΔCO_2), lac, $ScVO_2$, actual base excess (aBE), HCO_3 values were recorded. The correlations between these parameters were analysed. Pump flow was also recorded for each case.

STATISTICAL METHOD

Kolmogorov-Smirnov test was applied to determine the appropriate analysis method for the values taken in patients who were included in the study. All variables were not suitable for normal distribution ($p<0.05$). Changes of the measured variables according to time were performed by Friedman F test and Wilcoxon Marking test. Spearman correlation test was used to evaluate the variation between variables.

RESULTS

15 (37.5%) women and 25 (62.5%) men were included in the study. Other demographic data and some data related to the operation are shown in (Table 1).

When MAP, $ScVO_2$, ΔpCO_2, rSO_2, arterial HCO_3 values were compared in pairs according to time, the results were found to be significant ($p<0.05$).

When the mean values of lac at times T1, T2, T3 and T4 were 1.06±0.28, 0.94±0.26, 1.82±0.64, and 2.20±0.61, mean values of ΔpCO_2 were 7.97±1.15, 6.20±1.04, 5.84±1.27 ve 7.31±0.93 respectively. Other parameters and data about blood gas analysis are shown in (Table 2).

Between ΔpCO_2-lac values, positive correlation was found in only T4 and there was no corre-

TABLE 1: Demographic features and data about the operation.

Parameters	Mean	Standard Deviation
Age (year)	59.8	±12.17
Body surface area (m²)	1.89	±0.16
Weight (kg)	**76.85**	**±12.40**
Ejection fraction (EF) (%)	52.33	±5.33
Left atrium diameter (cm)	3.70	±0.35
Left ventricular diastolic dysfunction diameter (cm)	4.75	±0.39
Cardiopulmonary by-pass duration (minute)	77.1	±20.3
Cross-clamp duration (minute)	52.45	±13.5

lation between them at other times. Between rSO_2-lac values, negative correlation in T1, T3 and T4 was significant ($p<0.05$) and there was no significant correlation between rSO_2-ΔpCO_2 values at any time ($p>0.05$). Correlations between the parameters in the times of hypothermia (T3) and rewarming (T4) are shown in (Table 3).

Between ScVO2-lac there are negative correlations at all times, between HCO_3-lac there are negative correlations in T2, T3 and T4, between aBE-lac there are negative correlations in T3 and T4, between ΔpCO_2-$ScVO_2$ there is negative correlation in only T3, between rSO_2-Htc there are positive correlations in T1 and T4, between rSO_2-aBE there are positive correlations in T1, T3 and T4, between rSO_2-HCO_3 there are positive correlations in all times, between $ScVO_2$-HCO_3 there is positive correlation in only T4, between aBE-HCO3 there are positive correlations in T2, T3 and T4 were found to be significant ($p<0.05$). Other correlations between these parameters were found to be insignificant ($p>0.05$).

Correlations between the measurements of ΔpCO_2, rSO_2, $ScVO_2$, lac values at T2, T3, T4 and cross-clamp duration and CPB duration were found to be significant ($p<0.05$). The correlations of lac

TABLE 2: Hemodynamic parameters and results of blood gas analysis.

	T1 (before CPB) Mean±SD	T2 (CPB, normothermia) Mean ±SD	T3 (CPB, hypotermia) Mean ±SD	T4 (CPB, rewarming) Mean±SD
ΔpCO_2 (mmHg)	7.97±1.15	6.20±1.04	5.84±1.27	7.31±0.93
Lactate (mmol/L)	1.06±0.28	0.94±0.26	1.82±0.64	2.20±0.61
Actual base excess	0.14±1.52	0.84±1.71	0.18±1.64	-1.56±1.27
Arterial HCO_3	25.05±2.60	25.36±2.81	23.83±2.30	21.55±2.11
$ScVO_2$ (%)	77.18±3.99	75.67±3.82	71.06±3.33	67.23±3.83
Hematocrit (%)	35.73±3.81	28.29±3.36	28.02±2.65	29.83±2.26
Mean arterial pressure (mmHg)	79.85±5.71	69.80±4.53	66.28±3.35	70.98±3.29
rSO_2	70.45±3.28	74.03±3.04	66.90±3.35	71.15±2.64
Pump flow (L/m²/dk)	-	2.20±0.1	2.15±0.15	2.15±0.2

TABLE 3: The correlations between perfusion parameters in hypothermia (T_3) and rewarming (T_4).

	T1 (After induction)		T2 (Normothermia)		T3 (Hypothermia)		T4 (Rewarming)	
	p	Scc	p	Scc	p	Scc	p	Scc
Lac-$ScVO_2$	0.010*	-0.365	0.003*	-0.486	0.001*	-0.478	0.000*	-0.553
Lac-rSO_2	0.041*	-0.278	0.232	-0.119	0.021*	-0.322	0.001*	-0.462
Lac-HCO_3	0.150	-0.168	0.009*	-0.370	0.001*	-0.469	0.001*	-0.475
Lac-aBE	0.285	-0.093	0.159	-0.162	0.000*	-0.714	0.000*	-0.545
Lac- ΔpCO_2	0.447	-0.022	0.458	-0.017	0.065	0.244	0.038*	0.283
ΔpCO_2-$ScVO_2$	0.402	-0.041	0.107	-0.201	0.043*	-0.275	0.058	-0.252
rSO_2-Htc	0.019*	0.330	0.053	0.259	0.023*	0.318	0.045*	0.271
rSO_2-BE	0.021*	0.322	0.124	0.187	0.033*	0.293	0.000*	0.588
rSO_2-HCO_3	0.047*	0.268	0.037*	0.285	0.021*	0.322	0.008*	0.381
BE-HCO_3	0.055	0.256	0.003*	0.434	0.001*	0.482	0.001*	0.479
$ScVO_2$-HCO_3	0.313	0.080	0.164	0.159	0.094	0.212	0.005*	0.404
rSO_2-$ScVO_2$	0.002*	0.456	0.001*	0.458	0.005*	0.400	0.000*	0.616

*$p<0.05$: significant.

**Scc: Spearman correlation coefficient.

and ΔpCO_2 with cross-clamp and CPB durations were positive, whereas the correlations between $ScVO_2$ and rSO_2 with cross-clamp and CPB durations were negative.

DISCUSSION

The carbon dioxide partial pressure in the blood (pCO_2) can be used as a parameter reflecting the CO_2 content. Because there is a linear relationship between pCO_2 and CO_2 content. CO_2 is also dissolved in plasma and is also present in hemoglobin-bounded form. Therefore, there are some factors affecting pCO_2. These are: oxygenation, hemoglobin concentration, and as the blood pH is acidic or basic because it detects the disintegration of carbaminohemoglobin.[8] pCO_2 in central venous blood originates from the return of CO_2 from the tissues to the lungs for excretion. The CO_2 content in the tissues was determined by blood flow and CO_2 production. The change in CO_2 production or the change in blood flow changes the other variable.[9] Therefore, CO_2 production is affected by peripheral perfusion.

ΔpCO_2 is expected to be in the range of 2-5 mmHg under normal conditions. If the cardiac output gradually decreases, there will be an increase in veno-arterial pCO_2 (ΔpCO_2) if CO_2 production is stable. This is due to the accumulation of CO_2-rich blood coming from the peripheral tissue in the veins and the reduction of CO_2 elimination, as it cannot reach the pulmonary capillaries. ΔpCO_2 is more widened despite of decreased CO_2 production due to the decrease of cardiac output below critical levels which is the condition that relates with decreased oxygen demand due to overwhelming oxygen extraction capability of the body.[10]

As the oxygen level decreases in the peripheral tissue, CO_2 production increases anaerobically. Buffering of lactic acid produced by anaerobic reactions in the hypoxic tissue with bicarbonate (HCO_3) produces CO_2. Therefore, despite the decrease in oxygenation in peripheral tissue in the case of hypoperfusion, CO_2 production continues.[11]

As a result, an increase in ΔpCO_2 is expected in the case of decreased cardiac outflow and hypoperfusion. However, the increase in pCO_2 in tissues due to CO_2 produced by anaerobic metabolism caused by hypoperfusion should be considered to be higher than the increase in venous pCO_2.

Studies on ΔpCO_2, especially in sepsis and septic shock patients, are available.[12] In a study of 37 patients by Mecher et al. patients had ΔpCO_2 values greater than 6 mmHg and cardiac output were found to be low and ΔpCO_2 was decreased after fluid resuscitation.[4,13] In the study of Bakker et al. followed 64 patients with sepsis, low cardiac output of 15 patients also had high values of ΔpCO_2.[14] Therefore, ΔpCO_2 has been shown to be strongly associated with cardiac output in those studies. In some studies about septic patients, ΔpCO_2 was found to be associated with mortality.

In a study of Toraman et al. performed on 60 patients who underwent coronary artery bypass graft surgery; in the hypothermia period, due to the change in carbon dioxide solubility, the increase in ΔpCO_2 during CPB was not inversely proportional to inadequate blood flow and found a significant relationship between ΔpCO_2 and tissue perfusion parameters in periods other than hypothermia period.[15]

Another factor affecting pCO_2 is the solubility of CO2. The solubility of CO_2 is 20 times the solubility of oxygen. Therefore, CO_2 is more likely to be soluble.[10,11] While hypoperfusion was expected to increase ΔpCO_2, we found that ΔpCO2 decreased in the period of hypothermia (32º) (T3) in patients undergoing CPB technique. In T3, lactate elevation, HCO_3 and Htc decrease were observed as hypoperfusion findings, but ΔpCO_2 could not show the expected rise in hypoperfusion. This is due to the increased solubility of CO_2 in the blood due to hypothermia and therefore the CO_2 content does not reflect to the measured pCO_2.

In rewarming (36º) period (T4), we found an increase in ΔpCO2 while the increase in lactate level continued. The reason for this is that the accumulated CO_2 which is produced by anaerobic metabolism in the tissues is added to the venous circulation with increasing perfusion. A negative correlation between ΔpCO_2 and central venous O_2

($ScVO_2$) in T3 and a positive correlation with lac in T4 were found to be significant. However, the Spearman coefficients of these correlations were also low. Therefore, one of the results of this study is that ΔpCO_2 is not an early indicator of hypoperfusion.

The negative strong correlations of lactate with $ScVO_2$, cerebral oxygenation (rSO_2), HCO_3 and actual base excess (aBE) indicate that lactate gives the fastest and most accurate information about perfusion status.

Another aim of the study was to monitor the cerebral perfusion during CPB. For this purpose, a cerebral oximeter which works with a near-infrared spectrometer (NIRS) technique was used. There are several studies on the validity of NIRS monitoring.[16-18] In a randomized, prospective study consists of 200 patients in which Colak et al. investigated the effect of intraoperative cerebral oximetry follow-up on neurocognitive functions in coronary artery by-pass (CAB) surgery concluded that long-term cerebral desaturation may be considered as an important predictor of cognitive decline and they report that intraoperative cerebral oximetry monitoring and interventions to improve cerebral rSO_2 desaturation result in better cognitive consequences for patients.[17] In the study of Aydınlı et al. in the pediatric cardiac catheterization, percutaneous asd, vsd, pda closure were evaluated. They found that there was no difference between bilateral rSO_2 values in baseline, pre-and post-treatment periods, and the rSO_2 values were not affected by the decrease in blood pressure and hct values and the closure process.[19] In Türkyılmaz and his friends' study about 40 patients who underwent elective valve operation and coronary artery bypass grafting operation using CPB; they concluded that there were no significant differences in the parameters and NIRS measurements observed at the time intervals between the groups of patients with valve and coronary surgery.[13] In the study of Işıldak et al. evaluating the use of cerebral oximetry in hypoperfusion monitoring in pediatric cardiac surgery; they concluded that intraoperative monitoring of perfusion with cerebral oximetry during congenital heart surgery is a valuable indicator and they also report that right and left cerebral oximetry values have fallen in cases of tissue oxygenation was impaired (ex: hypotension, hemodilution, hypovolemia, anemia) and they determined that the values were corrected when the precautions were taken.[20]

In our study, rSO_2 values decreased to 58% and 59% in 2 patients during hypothermia (T3) period. In these cases, the pump flow was increased and cerebral oxygenation of the patients was kept above 60%. In these 2 cases which rSO_2 values were 58% and 59%, the duration of CPB was above the mean duration of 103 and 108 minutes, respectively. When the rSO_2 values decreased below 60% or there was a 20% decline from baseline values, hemodynamia, pump flow, hemoglobin and oxygenation were checked. These values were taken as the cut-off value for cerebral desaturation.[21] In addition, in two cases with cerebral desaturation, lac levels in T3 were above 2 mmol/L, and this was attributed to hypoperfusion status. In our study, rSO_2 had significant correlations with $ScVO_2$, lac, aBE, HCO_3, Htc, especially in hypothermia (T3) and rewarming (T4) periods, whereas no significant correlation was found with ΔpCO_2 at any time. Therefore, venoarterial CO_2 gradient is not an early indicator of hypoperfusion, nor is it a parameter associated with cerebral oxygenation status. There was a limiting condition with case numbers: because of limited number of coronary artery surgery patients and with exclusion of valve and aneurysm surgeries, 40 patients were included in this study.

CONCLUSION

$\Delta pCO2$ is not an early indicator of hypoperfusion in patients undergoing CPB. In particular, the lactate level is still the gold standard for reporting the perfusion status, in accordance with the literature. However, it should be noted that in cases where peripheral perfusion can be severely impaired, such as CPB, the perfusion status should be closely monitored and all perfusion markers should be evaluated together. As another result of the study, intraoperative cerebral oximetry monitoring is recommended so that the brain is not affected by hypoperfusion during CPB.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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